GLI ANTIDOTI NELLA PRATICA CLINICA: EFFICACIA, SICUREZZA E MODALITA' DI IMPIEGO

NAPOLI, 16 SETTEMBRE 2015

Intossicazioni da Farmaci: Moderni Orientamenti

G. Savoia

ARE YOU THE ONLY ONE TAKING YOUR MEDICINE

Medicine abuse is an **epidemic**

MOST TEENS

who report abuse of Rx pain relievers within the past year are getting them from family, friends and acquaintances.[1]

AN ESTIMATED 71,000 CHILDREN

18 and younger are seen in U.S. emergency departments each year because of unintentional medication poisonings. [2]

ABOUT 40% OF POISON EXPOSURES

reported to U.S. poison centers involve exposures to medications by children under age 6.[3]

IT'S NOT JUST YOU OR YOUR FAMILY YOU NEED TO WORRY ABOUT

PRESCRIPTION PAIN MEDICINE COULD ALSO BE MISUSED OR ABUSED IF YOUR HOME HAS:

- ☐ Young children, teenagers or babysitters
- ☐ Workers or delivery people inside
- ☐ House hunters who are looking around (if your house is for sale)
- ☐ Neighbors or friends coming in and out
- ☐ Prescription pain medicine on the kitchen counter, bedside table or another open space
- ☐ Prescription pain medicine you no longer need to take or that has expired

You can prevent abuse by taking steps to monitor, safeguard and properly dispose of your medicine.

PROTECT YOURSELF, YOUR FAMILY AND YOUR COMMUNITY

Very often, misuse and abuse begins at home. Are you and your family at risk? There are four steps you can take to protect yourself and the ones you love from accidental overdose or illegal use.

1 MONITOR YOUR MEDICATIONS

Take note of how many pills are in your medicine cabinet, keep track of your refills and follow directions on how to properly take your medicine. Remember, only you should take your prescription pain medicine.

2 SAFEGUARD YOUR MEDICATIONS

Secure your prescriptions the same way you would other valuables in your home, like cash or jewelry. Don't leave medicine lying around for anyone to take – keep it out of reach, out of sight and away from the public spaces in your house. Take prescriptions out of the medicine cabinet and secure them in a place only you know about. If possible, lock your medicine up to prevent anyone from tampering with or taking your medicine.

3 PROPERLY DISPOSE OF YOUR MEDICATIONS

Safely and promptly dispose of expired or unused prescription medicine. This is a critical step in helping to protect your family. Use at-home drug neutralization systems or return unused medication to an official take-back location.

4 TALK TO YOUR FAMILY

Share what you've learned about how to monitor, safeguard and dispose of your medicine with your family, friends and neighbors to make sure everyone plays their part in helping to keep your community safe.

Learn more:
http://www.alliancebpm.org/participate

Presidenza del Consiglio dei Ministri

CONFERENZA PERMANENTE PER I RAPPORTI TRA LO STATO, LE REGIONI E LE PROVINCE AUTONOME DI TRENTO E BOLZANO

Accordo, ai sensi dell'articolo 4 del decreto legislativo 28 agosto 1997, n. 281, tra il Governo, le Regioni e le Province autonome di Trento e di Bolzano concernente la definizione di attività ed i requisiti basilari di funzionamento dei Centri Antiveleni.

Rep. Atti n. 56/CSR del 28 febbraio 2008

LA CONFERENZA PERMANENTE PER I RAPPORTI TRA LO STATO, LE REGIONI E LE PROVINCE AUTONOME DI TRENTO E BOLZANO

Nella odierna seduta del 28 febbraio 2008:

Criteri di qualità e riservatezza dei Centri Antiveleni (CAV) (Parte D dell'allegato XI al D. Lgs n.65 del 14 marzo 2003)

- Locali e strutture dedicate esclusivamente al CAV
- Attività 24 ore al giorno
- Stato giuridico che caratterizza il CAV come struttura riconosciuta all'interno del Servizio sanitario nazionale
- Registrazione di tutti gli interventi effettuati
- Personale dedicato con adeguata idoneità professionale
- Accesso diretto alla consulenza telefonica per la popolazione in generale
- Strutture informatiche adeguate e non accessibili in rete
- Linea telefonica in entrata dedicata al CAV, nonché linea telefonica per il collegamento telematico
- Attività documentata per almeno un biennio in conformità alla risoluzione CEE 90/C 329/03 [2]
- Assunzione di responsabilità formale sull'utilizzo delle informazioni riservate da realizzare attraverso chiavi di accesso personalizzate

FUNZIONI E RUOLO DEI CENTRI ANTIVELENI

Le funzioni svolte dai CAV comprendono:

1. consulenza tossicologica specialistica, in urgenza e non, a mezzo telefono/fax/mail agli operatori sanitari (medici, farmacisti, infermieri, ecc…) delle Aziende Ospedaliere, delle ASL (in particolare dei Dipartimenti di Prevenzione e, laddove istituiti, dei Dipartimenti Veterinari), ai medici di medicina generale e pediatri di libera scelta, per la gestione dei pazienti con problematiche tossicologiche;

2. consulenza tossicologica specialistica per via telefonica alla popolazione in relazione al grado di pericolosità dell'esposizione, alla possibilità di trattamento domiciliare o alla eventuale necessità di ricovero;

3. attività clinica specialistica nelle varie forme previste dal Servizio Sanitario Nazionale (SSN) e dai Servizi Sanitari Regionali (SSR) al fine di assicurare la gestione diretta dei pazienti con intossicazione acuta presso il Pronto Soccorso e il Dipartimento d'Emergenza dell'ospedale in cui è operativo il Centro Antiveleni o presso il proprio reparto (ove presente);

4. attività di consulenza presso altri reparti dell'ospedale e visite specialistiche ambulatoriali (comprese le visite specialistiche di controllo post-dimissione ospedaliera, oppure per intossicazioni croniche o anche solo sospette);

5. identificazione delle necessità di tossicologia analitica clinica a livello nazionale, ai fini di una razionalizzazione delle risorse esistenti e di una loro migliore disponibilità;

6. reperimento, implementazione e continuo aggiornamento di banche dati tossicologiche e di banche dati relative a tutti i prodotti commercializzati in Italia (farmaci, prodotti per uso domestico, prodotti per uso agricolo, prodotti industriali, ecc....);

7. elaborazione statistico-epidemiologica dei dati relativi alle intossicazioni segnalate ai CAV, anche in collaborazione con altri Enti istituzionalmente competenti;

8. partecipazione alle attività di sorveglianza, vigilanza ed allerta, in collaborazione con il Ministero della Salute, le Regioni ed altri Enti istituzionalmente competenti;

9. monitoraggio del fabbisogno e valutazione di efficacia e sicurezza degli antidoti impiegati nel SSN e SSR;

10. attività di collaborazione, fatte salve le competenze dei diversi livelli istituzionali, nell'approvvigionamento, gestione e fornitura in urgenza a livello regionale e nazionale degli antidoti di difficile reperimento;

11. supporto tossicologico per la gestione delle urgenze ed emergenze sanitarie derivanti da incidenti chimici, convenzionali e non, ivi comprese le problematiche bioterroristiche, anche a supporto della Protezione Civile;

12. partecipazione ai gruppi di lavoro per l'elaborazione dei piani di emergenza, sulla base di quanto previsto dal D. Lgs 17 agosto 1999, n. 334 e successive modifiche e integrazioni, in stretto collegamento con le Regioni, le Agenzie di Sanità Pubblica e gli Osservatori Epidemiologici (laddove istituiti), ARPA/APPA, i competenti Servizi territoriali dei Dipartimenti di Prevenzione delle

ASL e con gli organismi competenti in materia di Protezione Civile, per situazioni di rischio particolari e nell'attività di bonifica ambientale;

13. supporto, collaborazione e consulenza nei confronti dei Dipartimenti di Prevenzione e, laddove istituiti, dei Dipartimenti Veterinari delle ASL, dei Laboratori di Sanità Pubblica, degli Istituti Zooprofilattici Sperimentali e dei Dipartimenti Provinciali delle ARPA/APPA per gli aspetti di competenza;

14. attività di formazione e aggiornamento in tossicologia clinica rivolta agli operatori sanitari del Servizio Sanitario Regionale e Nazionale;

15. attività didattica a livello interregionale rivolta a studenti di discipline sanitarie, nonché attività didattica per la prevenzione e il primo soccorso rivolta al pubblico, sia esso adulto che in età scolare;

16. attività di ricerca clinica e, ove possibile, preclinica, con particolare riferimento agli aspetti di diagnosi, di trattamento e di prevenzione;

17. realizzazione, mantenimento e continuo miglioramento, sia dal punto di vista funzionale che tecnologico e scientifico, di un sistema nazionale in grado di funzionare come una rete integrata sia nei servizi d'urgenza sia in quelli della prevenzione, sia a livello regionale che nazionale, nonché in grado di interfacciarsi a livello europeo.

Apparato/ sistema	Segni/ sintomi	Specifiche	Gravità e relativi valori di riferimento: (1=lieve; 2=moderata; 3=elevata 4=mortale)
CARDIOVASCOLARE			
	ALTERAZIONI ECG	alterazioni conduzione	
		aritmie sopreventricolari	
		aritmie ventricolari	
		ischemia/ necrosi	
	ANGOR/ DOLORE PRECORDIALE		
	ARRESTO CARDIORESPIRATORIO		
	BRADICARDIA		2 (40-50 adulti; 60-80 bambini; 3 (<40 adulti; <60 bambini);
	IPERTENSIONE		1 (100-109 minima; 160-180 massima), 2 (110-119 minima; 180-209 massima), 3 (>120 minima; >210 massima);
	IPOTENSIONE		1/2 (<80/<60); 3 (<70/<40)
	ISCHEMIA CARDIACA ACUTA		
	TACHICARDIA		2 (140-180 adulti; 160-190 bambini); 3 (>180 adulti; >190 bambini);
	CARDIOPALMO		
	SINCOPE		
	STATO DI SHOCK NON TRAUMATICO		
	ALTRO		

RAPPORTI ISTISAN 14|13

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Sistema informativo nazionale per la sorveglianza delle esposizioni pericolose e delle intossicazioni: casi rilevati nel 2010

Quinto rapporto annuale

L. Settimi, F. Davanzo, E. Urbani, F. Giordano, L. Cossa

Tabella 5. Circostanza di esposizione e classe di età dei casi esaminati dal CAV di Milano nel 2010. Dati SIN-SEPI

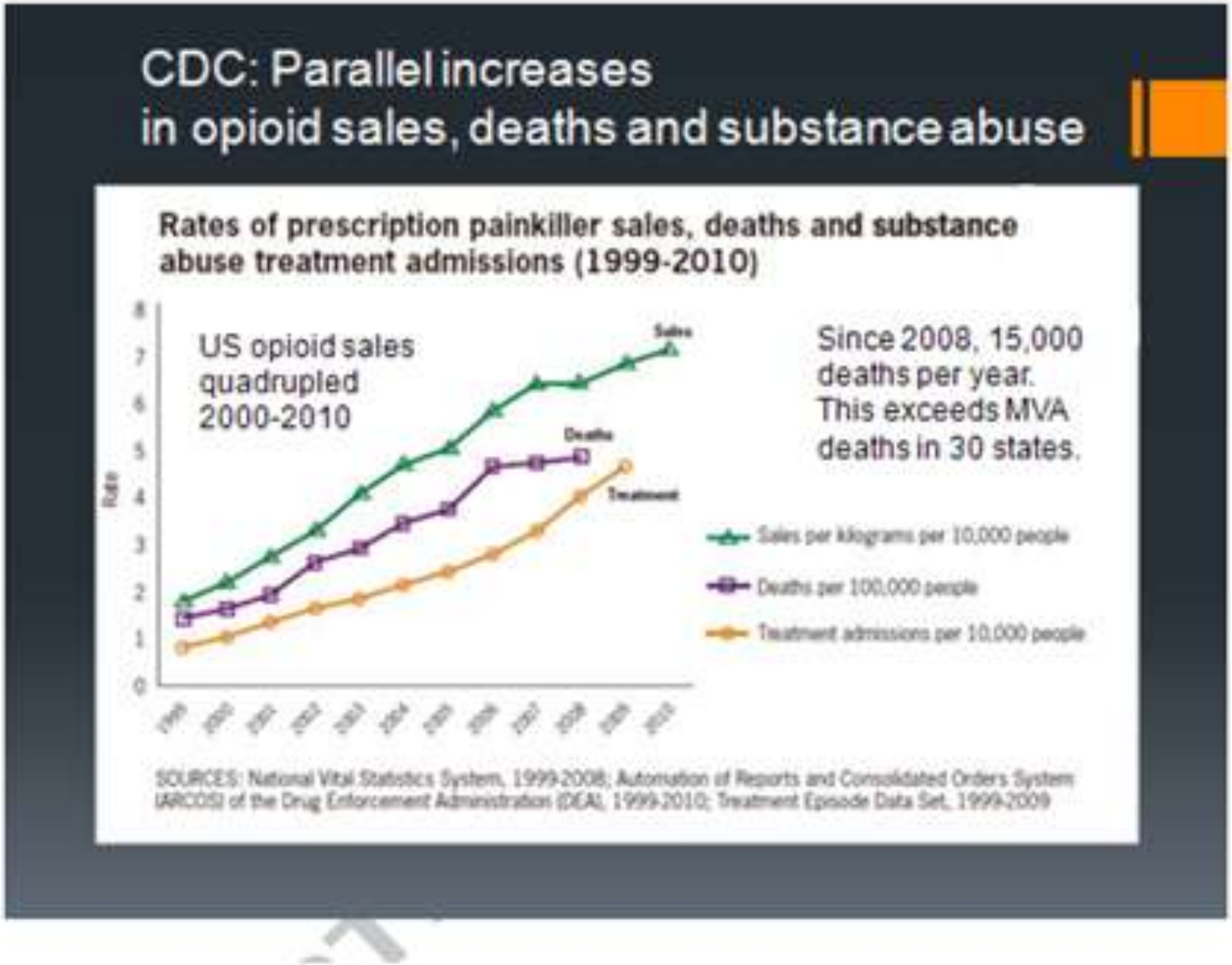
Circostanza	Totale casi		Classe di età (anni)							
			< 6		6-19		> 19		Non nota	
	n.	%	n.	%	n.	%	n.	%	n.	%
Accidentale	**31.590**	**77,7**	**18.119**	**99,0**	**2.769**	**73,6**	**9.047**	**54,3**	**1.655**	**84,5**
Accesso incontrollato	18.323	45,1	15.667	85,6	1.290	34,3	1.055	6,3	311	**85,0**
Errore terapeutico	3.579	8,8	1.626	8,9	475	12,6	1.396	8,4	82	16,0
Travaso	2.008	4,9	229	1,3	214	5,7	1.457	8,7	108	4,2
Alimentare	1.476	3,6	82	0,4	130	3,5	863	5,2	401	5,5
Occupazionale	1.070	2,6	0	0,0	21	0,6	894	5,4	155	20,6
Ambientale	552	1,4	80	0,4	78	2,1	218	1,3	176	8,0
Uso improprio	685	1,7	13	0,1	57	1,5	569	3,4	46	9,0
Incidente di trasporto	2	0,0	0	0,0	0	0,0	2	0,0	0	2,4
Generica/non nota	3.895	9,6	422	2,3	504	13,4	2.593	15,6	376	0,0
Intenzionale	**7.905**	**19,4**	**0**	**0,0**	**846**	**22,5**	**6.890**	**41,4**	**169**	*19,3*
Tentato suicidio	6.514	16,0	0	0,0	614	16,3	5.787	34,7	113	**8,7**
Abuso	906	2,2	0	0,0	160	4,3	712	4,3	34	5,8
Automedicazione	357	0,9	0	0,0	41	1,1	301	1,8	15	1,7
Non nota	128	0,3	0	0,0	31	0,8	90	0,5	7	0,8
Dolosa	**59**	**0,1**	**2**	**0,0**	**7**	**0,2**	**37**	**0,2**	**13**	*0,4*
Reazione avversa	**498**	**1,2**	**74**	**0,4**	**63**	**1,7**	**338**	**2,0**	**23**	**0,7**
Non nota	**610**	**1,5**	**100**	**0,5**	**77**	**2,0**	**345**	**2,1**	**88**	**1,2**
Totale	**40.662**	**100,0**	**18.295**	**100,0**	**3.762**	**100,0**	**16.657**	**100,0**	**1.948**	**100,0**
% riga		*100,0*		*45,0*		*9,3*		*41,0*		*4,8*

Tabella 10. Categorie secondarie di *Farmaci* e *Non farmaci* più frequentemente rilevate e classe di età dei casi di esposizione esaminati nel 2010. Dati SIN-SEPI

Categoria principale di agente Categoria secondaria	Totale casi		Classe di età (anni)							
			<6		6-19		>19		Non nota	
	n.	%[a]	n.	%[b]	n.	%[b]	n	%[b]	n	%[b]
Farmaci										
Sedativi/ipnotici/antipsicotici	4.455	11,0	309	1,7	315	8,4	3.741	22,5	90	4,6
Analgesici	2.706	6,7	1.162	6,4	365	9,7	1.140	6,8	39	2,0
Antidepressivi	2.081	5,1	147	0,8	144	3,8	1.755	10,5	35	1,8
Cardiovascolari	1.351	3,3	479	2,6	73	1,9	773	4,6	26	1,3
Anticonvulsivanti	1.270	3,1	93	0,5	90	2,4	1.068	6,4	19	1,0
Antimicrobici	1.260	3,1	598	3,3	183	4,9	451	2,7	28	1,4
Preparati per uso topico	1.235	3,0	502	2,7	117	3,1	579	3,5	37	1,9
Ormoni/antagonisti ormonali	1.128	2,8	698	3,8	95	2,5	316	1,9	19	1,0
Gastrointestinali	908	2,2	419	2,3	106	2,8	371	2,2	12	0,6
Antistaminici	716	1,8	441	2,4	122	3,2	146	0,9	7	0,4
Antiasmatici	612	1,5	428	2,3	61	1,6	110	0,7	13	0,7
Integratori/erboristici/omeopatici	508	1,2	291	1,6	47	1,2	155	0,9	15	0,8
Stimolanti e droghe da strada	438	1,1	10	0,1	78	2,1	334	2,0	16	0,8
Tosse/malattie da raffreddamento	366	0,9	257	1,4	43	1,1	60	0,4	6	0,3
Profilassi carie	303	0,7	274	1,5	23	0,6	0	0,0	6	0,3
Anticoagulanti	280	0,7	105	0,6	13	0,3	158	0,9	4	0,2
Preparati occhi/orecchi/naso/gola	270	0,7	170	0,9	33	0,9	57	0,3	10	0,5
Vitamine	241	0,6	163	0,9	18	0,5	58	0,3	2	0,1
Trattamento dipendenze	213	0,5	16	0,1	9	0,2	182	1,1	6	0,3

Non farmaci										
Prodotti di uso domestico	7.596	18,7	3.921	21,4	440	11,7	2.956	17,7	279	14,3
Antiparassitari	1.956	4,8	788	4,3	120	3,2	927	5,6	121	6,2
Cosmetici/cura della persona	1.952	4,8	1.473	8,1	103	2,7	335	2,0	41	2,1
Corpi estranei	1.831	4,5	1.459	8,0	214	5,7	98	0,6	60	3,1
Alcoli/bevande alcoliche	1.107	2,7	152	0,8	117	3,1	800	4,8	38	2,0
Funghi	997	2,5	57	0,3	78	2,1	618	3,7	244	12,5
Piante	876	2,2	561	3,1	85	2,3	156	0,9	74	3,8
Alimenti/acqua contaminata	845	2,1	193	1,1	102	2,7	377	2,3	173	8,9
Morsi/punture	729	1,8	104	0,6	121	3,2	460	2,8	44	2,3
Colori/arte/cancelleria	728	1,8	551	3,0	137	3,6	25	0,2	15	0,8
Fumi/gas/vapori	662	1,6	93	0,5	88	2,3	273	1,6	208	10,7
Sostanze chimiche	503	1,2	149	0,8	34	0,9	277	1,7	43	2,2
Deodoranti ambientali/WC	517	1,3	468	2,6	15	0,4	27	0,2	7	0,4
Idrocarburi	492	1,2	84	0,5	66	1,8	309	1,9	33	1,7
Pitture sverniciatori	366	0,9	93	0,5	39	1,0	212	1,3	22	1,1
Prodotti di uso industriale	324	0,8	46	0,3	32	0,9	206	1,2	40	2,1
Batterie	318	0,8	210	1,1	37	1,0	51	0,3	20	1,0
Colle	314	0,8	174	1,0	43	1,1	76	0,5	21	1,1
Fertilizzanti/Integratori	313	0,8	87	0,5	30	0,8	169	1,0	27	1,4
Tabacco	299	0,7	276	1,5	8	0,2	12	0,1	3	0,2
Olii essenziali	213	0,5	158	0,9	18	0,5	34	0,2	3	0,2
Esplosivi accendifuoco	191	0,5	165	0,9	7	0,2	12	0,1	7	0,4

Figure 2: prescription opioid sales, deaths and substance abuse admissions in US



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Review Article

Poisoning with illicit substances: toxicology for the anaesthetist

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Summary

The consumption of illicit substances represents a considerable threat to the health and wellbeing of particular sectors of our communities. Hospitalisation is sometimes required for the treatment of the direct toxic effects of the drugs as well as for injuries sustained while under their influence. Although poisoning with 'traditional' substances of abuse such as opioids, cocaine and cannabis still predominate in terms of numbers, the availability and use of new psychoactive substances are on the rise. These latter agents, some of which began life as failed pharmaceutical products, have enjoyed renewed status as recreational stimulants, entactogens or hallucinogens, properties that originally precluded them from legitimate use. These drugs may act by enhancing endogenous release of neurotransmitters, inhibiting their reuptake back into neurons or having direct effects on receptors, and may involve adrenergic, dopaminergic or serotonergic systems. The use of intravenous lipid emulsion for the symptomatic treatment of drug overdose has become a fertile ground for research and may hold promise as a non-specific treatment for poisoning with illicit substances. Dexmedetomidine, an α_2-receptor agonist with a central sympatholytic effect, may be able to counteract the cardiovascular and central nervous system overstimulation that may accompany stimulant toxicity.

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cannabinoidi

Agitazione

Convulsioni

Broncopasmo

Edema uvulare

Benzodiazepine, alfa2agonisti

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Anaesthesia, 2010, **65**, pages 163–166 doi:10.1111/j.1365-2044.2009.06189

ORIGINAL ARTICLE

Cocaine-related admissions to an intensive care unit: a five-year study of incidence and outcomes

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Summary

Cocaine misuse is increasing and it is evidently considered a relatively safe drug of abuse in Ireland. To address this perception, we reviewed the database of an 18-bed Dublin intensive care unit, covering all admissions from 2003 to 2007. We identified cocaine-related cases, measuring hospital mortality and long-term survival in early 2009. Cocaine-related admissions increased from around one annually in 2003–05 to 10 in 2007. Their median (IQR [range]) age was 25 (21–35 [17–47]) years and 78% were male. The median (IQR [range]) APACHE II score was 16 (11–27 [5–36]) and length of intensive care stay was 5 (3–9 [1–16]) days. Ten patients died during their hospital stay. A further five had died by the time of follow-up, a median of 24 months later. One was untraceable. Cocaine toxicity necessitating intensive care is increasingly common in Dublin. Hospital mortality in this series was 52%. These findings may help to inform public attitudes to cocaine.

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Case	Age	Length of stay; days	Sex	Apache II score	Hospital outcome	Current status	Reason for intensive care admission
1	19	4	Male	10	Survived	Dead	Cardiac arrest
2	44	10	Male	22	Died	Dead	Cardiac arrest
3	24	8	Female	27	Died	Dead	Cardiac arrest
4	28	2	Female	13	Died	Dead	Cardiac arrest
5	17	16	Male	16	Died	Dead	Comatose
6	29	5	Male	12	Died	Dead	Comatose
7	21	5	Male	5	Survived	Dead	Comatose
8	33	2	Female	16	Survived	Alive	Aspiration injury
9	24	8	Male	29	Survived	Dead	Comatose
10	18	1	Female	27	Died	Dead	Comatose
11	25	2	Male	9	Died	Dead	Aspiration injury
12	21	5	Male	16	Survived	Dead	Comatose
13	27	3	Male	26	Died	Dead	Comatose
14	21	9	Male	36	Survived	Alive	Seizure
15	43	2	Male	22	Died	Dead	Cardiac arrest
16	47	4	Male	21	Died	Dead	Comatose
17	23	7	Male	6	Survived	Dead	Cardiac arrest
18	36	9	Male	28	Survived	Unknown	Seizure
19	41	13	Male	5	Survived	Alive	Seizure

Table 1 Characteristics of patients and outcome data for cocaine-related intensive care admissions from 2003 to 2007.

Cocaina

- > noradrenalina e dopamina
- Ipertensione , tachicardia , ipertermia
- Agitazione psicomotoria ,convulsioni

- Alfa e betablocco challenge
- Tachicardia riflessa da vasodilatatori
- No ketamina
- Si benzodiazepine e dexmedetomidina

Anfetamine ed ecstasy

- *Recettori adrenergici*
- *Recettori NMDA*
- *> serotonina, dopamina e noradrenalina*
- *Iperpiressia, rabdomiolisi,insufficienza epatica*
- *Sindrome serotoninergica*

- *Raffreddamento ? Dantrolene*
- *Controllo stato iperadrenergico*
- *Controllo idratazione*

Nuovi composti

- *Catinone*
- *Piperazina*
- *Triptamina*

Part 12: Cardiac Arrest in Special Situations

2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Terry L. Vanden Hoek, Chair; Laurie J. Morrison; Michael Shuster; Michael Donnino; Elizabeth Sinz; Eric J. Lavonas; Farida M. Jeejeebhoy; Andrea Gabrielli

S840 *Circulation* November 2, 2010

Part 12.7: Cardiac Arrest Associated With Toxic Ingestions

Table. Common Toxidromes*

Cardiac Signs		
Tachycardia and/or Hypertension	Bradycardia and/or Hypotension	Cardiac Conduction Delays (Wide QRS)
Amphetamines	Beta blockers	Cocaine
Anticholinergic drugs	Calcium channel blockers	Cyclic antidepressants
Antihistamines	Clonidine	Local anesthetics
Cocaine	Digoxin and related glycosides	Propoxyphene
Theophylline/caffeine	Organophosphates and carbamates	Antiarrhythmics (e.g., quinidine, flecainide)
Withdrawal states		

CNS/Metabolic Signs		
Seizures	CNS and/or Respiratory Depression	Metabolic Acidosis
Cyclic antidepressants	Antidepressants (several classes)	Cyanide
Isoniazid	Benzodiazepines	Ethylene glycol
Selective and non-selective norepinephrine reuptake inhibitors (eg, bupropion)	Carbon monoxide	Metformin
Withdrawal states	Ethanol	Methanol
	Methanol	Salicylates
	Opioids	
	Oral hypoglycemics	

*Differential diagnosis lists are partial.

Dries and Endorf *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2013, **21**:31
http://www.sjtrem.com/content/21/1/31

SCANDINAVIAN JOURNAL OF
trauma, resuscitation
& emergency medicine

REVIEW **Open Access**

Inhalation injury: epidemiology, pathology, treatment strategies

David J Dries[1*] and Frederick W Endorf[2]

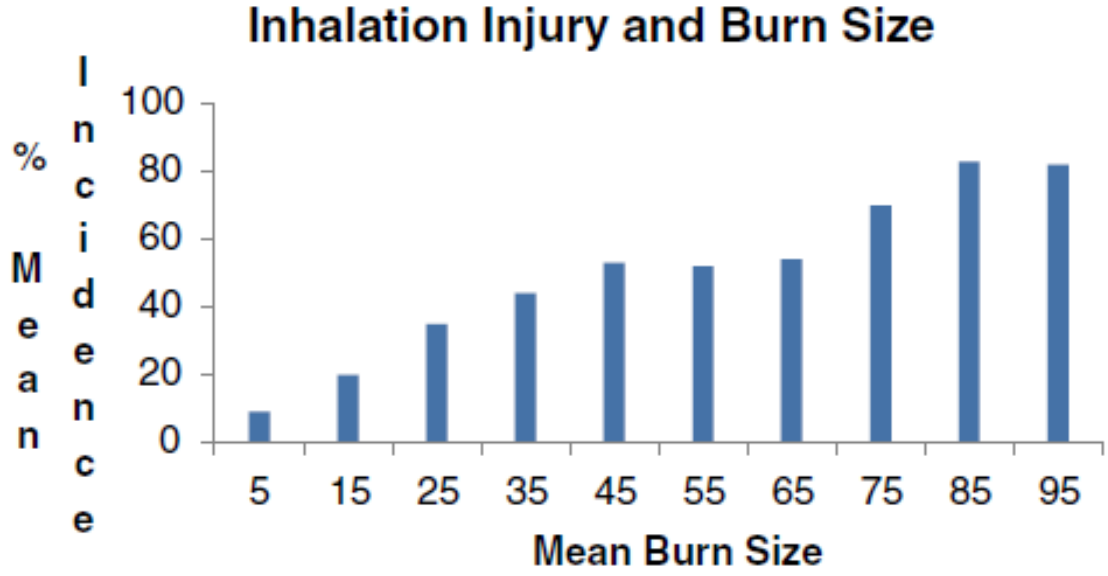

Figure 1 Relationship between burn size and incidence of inhalation injury illustrates the rise in occurrence of inhalation injury with increasing burn size [5].

Abstract

Lung injury resulting from inhalation of smoke or chemical products of combustion continues to be associated with significant morbidity and mortality. Combined with cutaneous burns, inhalation injury increases fluid resuscitation requirements, incidence of pulmonary complications and overall mortality of thermal injury. While many products and techniques have been developed to manage cutaneous thermal trauma, relatively few diagnosis-specific therapeutic options have been identified for patients with inhalation injury. Several factors explain slower progress for improvement in management of patients with inhalation injury. Inhalation injury is a more complex clinical problem. Burned cutaneous tissue may be excised and replaced with skin grafts. Injured pulmonary tissue must be protected from secondary injury due to resuscitation, mechanical ventilation and infection while host repair mechanisms receive appropriate support. Many of the consequences of smoke inhalation result from an inflammatory response involving mediators whose number and role remain incompletely understood despite improved tools for processing of clinical material. Improvements in mortality from inhalation injury are mostly due to widespread improvements in critical care rather than focused interventions for smoke inhalation.

Morbidity associated with inhalation injury is produced by heat exposure and inhaled toxins. Management of toxin exposure in smoke inhalation remains controversial, particularly as related to carbon monoxide and cyanide. Hyperbaric oxygen treatment has been evaluated in multiple trials to manage neurologic sequelae of carbon monoxide exposure. Unfortunately, data to date do not support application of hyperbaric oxygen in this population outside the context of clinical trials. Cyanide is another toxin produced by combustion of natural or synthetic materials. A number of antidote strategies have been evaluated to address tissue hypoxia associated with cyanide exposure. Data from European centers supports application of specific antidotes for cyanide toxicity. Consistent international support for this therapy is lacking. Even diagnostic criteria are not consistently applied though bronchoscopy is one diagnostic and therapeutic tool. Medical strategies under investigation for specific treatment of smoke inhalation include beta-agonists, pulmonary blood flow modifiers, anticoagulants and antiinflammatory strategies. Until the value of these and other approaches is confirmed, however, the clinical approach to inhalation injury is supportive.

Keywords: Smoke inhalation, Burns, Carbon monoxide, Cyanide, Bronchoscopy

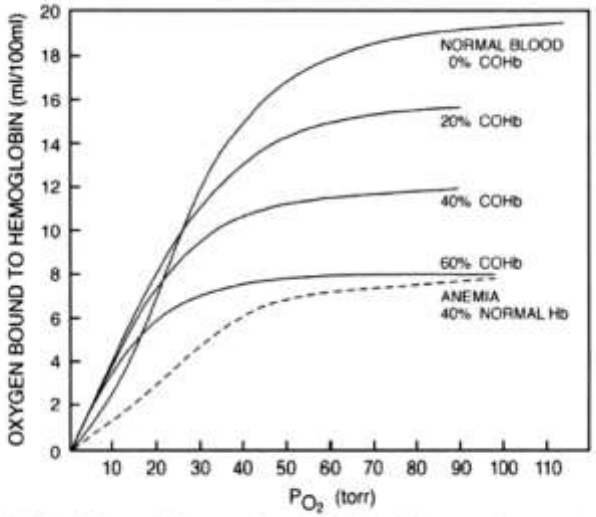

Figure 5 Carboxyhemoglobin-induced changes in the oxygen-hemoglobin dissociation curve. Oxygen-carrying capacity is markedl diminished when carboxyhemoglobin values reach 40% to 50%. In addition, the leftward displacement of the oxygen-hemoglobin dissoci curve makes the oxygen that is bound to hemoglobin less available for delivery to tissues [3].

Table 3 Comparison by P:F ratio

	P:F <350 (30 Patients)	P:F >350 (30 Patients)	*P* Value
mL/kg/%TBSA	7.4 (±0.4)	5.9 (±0.5)	.03
Ventilator days	12.2 (±2.4)	0.9 (±1.5)	.21
Survival	18 (60%)	23 (77%)	.17

Endorf and Gamelli [25].

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Table 1 Bronchoscopic criteria used to grade inhalation injury

Grade 0 (No Injury):	Absence of carbonaceous deposits, erythema, edema, bronchorrhea, or obstruction.
Grade 1 (Mild Injury):	Minor or patchy areas of erythema, carbonaceous deposits in proximal or distal bronchi. [any or combination]
Grade 2 (Moderate Injury):	Moderate degree of erythema, carbonaceous deposits, bronchorrhea, with or without compromise of the bronchi. [any or combination]
Grade 3 (Severe Injury):	Severe inflammation with friability, copious carbonaceous deposits, bronchorrhea, bronchial obstruction. [any or combination]
Grade 4 (Massive Injury):	Evidence of mucosal sloughing, necrosis, endoluminal obliteration. [any or combination]

Endorf and Gamelli [25].

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Table 2 Comparison for bronchoscopic grade of inhalation injury

	Group 1 (Grades 0 and 1) 25 Patients	Group 2 (Grades 2, 3, 4) 35 Patients	*P* Value
mL/kg/%TBSA	6.6 (±0.7)	6.7 (±0.4)	.88
Ventilator days	8.6 (±1.4)	12.8 (±2.2)	.11
Survival	21 (84%)	20 (57%)	.03
Initial compliance	49.9 (±4.4)	49.7 (±3.1)	.98
Initial P:F Ratio	371.5 (±32)	329.7 (±29)	.33

Endorf and Gamelli [25].

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SYSTEMATIC REVIEW

Second-Generation Antipsychotics and Neuroleptic Malignant Syndrome: Systematic Review and Case Report Analysis

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Abstract

Background Neuroleptic malignant syndrome (NMS) is a rare, severe, idiosyncratic adverse reaction to antipsychotics. Second-generation antipsychotics (SGAs) were originally assumed to be free from the risk of causing NMS, however several cases of NMS induced by SGAs (SGA-NMS) have been reported.

Objectives The aim of this study was to systematically review available studies and case reports on SGA-NMS and compare the presentation of NMS induced by different SGAs.

Data Sources Citations were retrieved from PubMed up to November 2013, and from reference lists of relevant citations.

Study Eligibility Criteria Eligibility criteria included (a) primary studies reporting data on NMS, with at least 50 % of the sample receiving SGAs; or (b) case reports and case reviews reporting on NMS induced by SGA monotherapy, excluding those due to antipsychotic withdrawal.

Study Appraisal and Synthesis Methods A standardized method for data extraction and coding was developed for the analysis of eligible case reports.

Results Six primary studies and 186 individual cases of NMS induced by SGAs were included. Primary studies suggest that SGA-NMS is characterized by lower incidence, lower clinical severity, and less frequent lethal outcome than NMS induced by first-generation antipsychotics. Systematic analysis of case reports suggests that even the most recently marketed antipsychotics are not free from the risk of inducing NMS. Furthermore, clozapine-, aripiprazole- and amisulpride-induced NMS can present with atypical features more frequently than other SGA-NMS, i.e. displaying less intense extrapyramidal symptoms or high fever.

Limitations Case reports report non-systematic data, therefore analyses may be subject to bias.

Conclusions and Implications of Key Findings Clinicians should be aware that NMS is virtually associated with all antipsychotics, including those most recently marketed. Although apparently less severe than NMS induced by older antipsychotics, SGA-NMS still represent a relevant clinical issue.

Electronic supplementary material The online version of this article (doi:10.1007/s40268-014-0078-0) contains supplementary material, which is available to authorized users.

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Key Points

Neuroleptic malignant syndrome (NMS) induced by second-generation antipsychotics is characterized by lower incidence, lower clinical severity, and less frequent lethal outcome than NMS induced by first-generation antipsychotics.

Even the most recently marketed antipsychotics are not free from the risk of inducing NMS.

Clozapine-, aripiprazole- and amisulpride-induced NMS can present with atypical features more frequently than other SGA-NMS, i.e. displaying less intense extrapyramidal symptoms or high fever.

Langan et al. BMC Psychiatry 2012, 12:214
http://www.biomedcentral.com/1471-244X/12/214

BMC Psychiatry

DATABASE Open Access

Antipsychotic dose escalation as a trigger for Neuroleptic Malignant Syndrome (NMS): literature review and case series report

Julie Langan[1], Daniel Martin[1], Polash Shajahan[2] and Daniel J Smith[1*]

Abstract

Background: "Neuroleptic malignant syndrome" (NMS) is a potentially fatal idiosyncratic reaction to any medication which affects the central dopaminergic system. Between 0.5% and 1% of patients exposed to antipsychotics develop the condition. Mortality rates may be as high as 55% and many risk factors have been reported. Although rapid escalation of antipsychotic dose is thought to be an important risk factor, to date it has not been the focus of a published case series or scientifically defined.

Description: We aimed to identify cases of NMS and review risk factors for its development with a particular focus on rapid dose escalation in the 30 days prior to onset. A review of the literature on rapid dose escalation was undertaken and a pragmatic definition of "rapid dose escalation" was made. NMS cases were defined using DSM-IV criteria and systematically identified within a secondary care mental health service. A ratio of titration rate was calculated for each NMS patient and "rapid escalators" and "non rapid escalators" were compared. 13 cases of NMS were identified. A progressive mean dose increase 15 days prior to the confirmed episode of NMS was observed (241.7 mg/day during days 1–15 to 346.9 mg/day during days 16–30) and the mean ratio of dose escalation for NMS patients was 1.4. Rapid dose escalation was seen in 5/13 cases and non rapid escalators had markedly higher daily cumulative antipsychotic dose compared to rapid escalators.

Conclusions: Rapid dose escalation occurred in less than half of this case series (n = 5, 38.5%), although there is currently no consensus on the precise definition of rapid dose escalation. Cumulative antipsychotic dose – alongside other known risk factors - may also be important in the development of NMS.

Keywords: Neuroleptic malignant syndrome, NMS, Rapid dose escalation, Rapid dose titration, Antipsychotics

Table 1 DSM IV Research criteria for neuroleptic malignant syndrome

A. Development of severe musde rigidity and elevated temperature associated with the use of neuroleptic medication

B. Two (or more) of the following

   a. diaphoresis,

   b. dysphagia,

   c. tremor,

   d. incontinence,

   e. changes in level of consciousness (ranging from confusion to coma),

   f. mutism,

   g. tachycardia,

   h. elevated or labile blood pressure,

   i. leukocytosis

   j. Laboratory evidence of muscle injury (e.g. elevated CPK creatinine phosphokinase).

C. The symptoms in criteria A and B are not due to another substance, neurological or general medical condition

D. The symptoms in A and B are no better accounted for by a mental disorder

Table 2 Antipsychotic chlorpromazine equivalents

Medication (mg)	Chlorpromazine Equivalence (mg)
Chlorpromazine 100	100
Quetiapine 133.3	100
Amisulpiride 100	100
Olanzapine 5	100
Aripiprazole 7.5	100
Risperidone 2	100
Clozapine 200	100
Haloperidol 3	100
Sulpiride 200	100
ClopixolAccuphase (zuclopenthixol acetate) 100	100

CLINICAL CONCEPTS AND COMMENTARY

Bruno Riou, M.D., Ph.D., Editor

Lipid Emulsion Infusion

Resuscitation for Local Anesthetic and Other Drug Overdose

Guy L. Weinberg, M.D.*

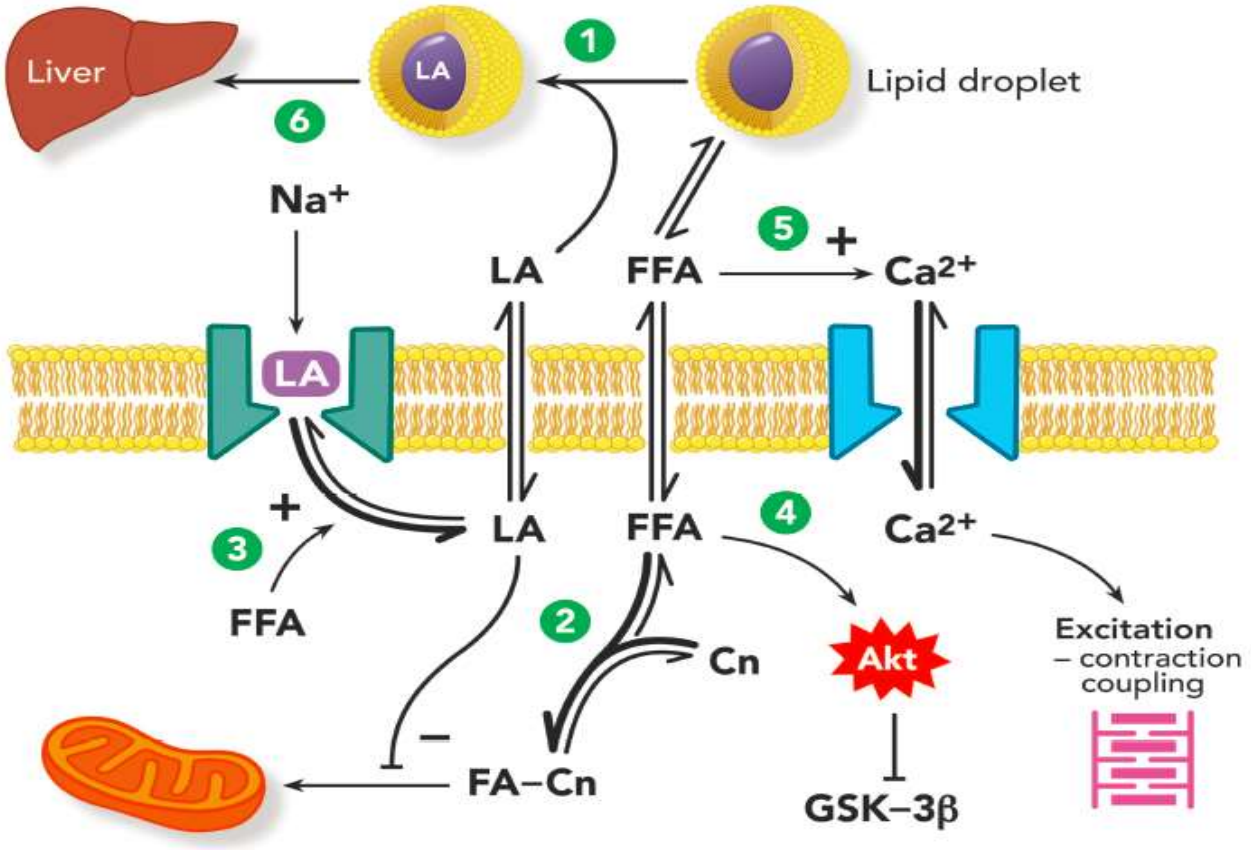

Fig. 1. Proposed mechanisms of lipid resuscitation. After infusion, the lipid emulsion exists in the blood as emulsified oil droplets or multilamellar vesicles. (1) Capture of local anesthetic (lipid sink); (2) Increased fatty acid uptake by mitochondria (metabolic effect); (3) Inteference with local anesthetic binding of sodium channels (membrane effect); (4) Activation of Akt cascade leading to inhibition of GSK-3β (cytoprotection); (5) Promotion of calcium entry *via* voltage-dependent calcium channels (ionotropic/inotropic; can also involve mitochondrial calcium dynamics); (6) Accelerated shunting (pharmacokinetic effects). Akt = a serine/threonine protein kinase important in cell survival, proliferation, and migration, also called protein kinase B; Ca^{2+} = calcium ion; Cn = carnitine; FA-Cn: fatty acyl carnitine; FFA = free fatty acids; GSK-3β = glycogen synthase kinase (phophorylates and thereby inhibits glycogen synthase; inhibition of GSK-3β has been implicated in preventing myocardial ischemia–reperfusion injury); LA = local anesthetic; Na^+ = sodium ion.

Other Mechanisms

Mottram *et al.*[25] showed in a heterologous tissue culture expression system that free fatty acids reduced bupivacaine inhibition of sodium channel currents. They suggest that modulation of cardiac sodium channels could contribute to reversal of bupivacaine toxicity. Taking a much different approach, Rahman *et al.*[26] showed that lipid infusion attenuates cardiac ischemia reperfusion injury. They found that postischemic infusion of lipid in rodents, as observed in the experiments with metabolic inhibitors, reduced the likelihood of mitochondrial permeability transition and apoptosis. It is very possible that such activation of cytoprotective pathways contributes to the clinically observed benefit of lipid-based resuscitation, a much more complex clinical phenomenon than was initially appreciated. We can now consider separating the results of lipid infusion into intracellular (metabolic, signaling), intravascular (partitioning, sink), and membrane (channel) effects. Future scientific investigation will hopefully identify all the underlying consequences of lipid emulsion infusion and determine their relative contributions to reversing drug overdose.

Treatment of Local Anesthetic Systemic Toxicity (LAST)

Guy L. Weinberg, MD

TABLE 1. Recommendations for Treatment of Local Anesthetic Systemic Toxicity (LAST)

- If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia and acidosis, which are known to potentiate LAST (I; B).
- If seizures occur, they should be rapidly halted with benzodiazepines. If benzodiazepines are not readily available, small doses of propofol or thiopental are acceptable. Future data may support the early use of lipid emulsion for treating seizures (I; B).
- Although propofol can stop seizures, large doses further depress cardiac function; propofol should be avoided when there are signs of cardiovascular compromise (III; B). If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxemia (I; C).
- If cardiac arrest occurs, we recommend standard advanced cardiac life support with the following modifications:
  - If epinephrine is used, small initial doses (10- to 100-μg boluses in adults) are preferred (IIa; C).
  - Vasopressin is not recommended (IIB; B).
  - Avoid calcium channel blockers and beta-adrenergic receptor blockers (III; C).
  - If ventricular arrhythmias develop, amiodarone is preferred (IIa; B); treatment with local anesthetics (lidocaine or procainamide) is not recommended (III; C).
- Lipid emulsion therapy (IIa; B):
  - Consider administering at the first signs of LAST, after airway management.
  - Dosing
    - 1.5 mL/kg 20% lipid emulsion bolus
    - Infusion of 0.25 mL/kg per minute, continued for at least 10 mins after circulatory stability is attained
    - If circulatory stability is not attained, consider giving another bolus and increasing infusion to 0.5 mL/kg per minute
    - Approximately 10 mL/kg lipid emulsion over 30 mins is recommended as the upper limit for initial dosing.
- Propofol is not a substitute for lipid emulsion (III; C).
- Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of cardiopulmonary bypass (IIa; C). Because there can be considerable lag in beginning cardiopulmonary bypass, it is reasonable to notify the closest facility capable of providing it when cardiovascular compromise is first identified during an episode of LAST.

The class of recommendation and level of evidence for each intervention are given in parenthesis.

ORIGINAL ARTICLE

Epinephrine Administration in Lipid-Based Resuscitation in a Rat Model of Bupivacaine-Induced Cardiac Arrest

Optimal Timing

Zhousheng Jin, BS, Yun Xia, MD, PhD,† Fangfang Xia, BS,* Cong Wu, BS,* Zhe Chen, BS,* Fubei Nan, BS,* Bingjing Wu, BS,* Li Wan, MD,‡ Xianqin Wang, PhD,§ Thomas J. Papadimos, MD, MPH,† and Xuzhong Xu, MD**

Conclusions: In the rat model of bupivacaine-induced cardiac arrest, the optimal timing for the administration of epinephrine to produce best outcomes of successful cardiopulmonary resuscitation is immediately after the completion of the lipid emulsion bolus. This optimal timing/therapeutic window is of paramount importance.

(*Reg Anesth Pain Med* 2015;40: 223–231)

Phosphorylation of GSK-3β Mediates Intralipid-induced Cardioprotection against Ischemia/Reperfusion Injury

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What We Already Know about This Topic

- Activation of the Reperfusion Injury Salvage Kinases pathway protects against myocardial infarction and delays opening of the mitochondrial permeability transition pore
- Intralipid may have cardioprotective effects, but the magnitude of and mechanisms responsible for these actions are unclear

 Anesthesiology 2011; 115:242–53

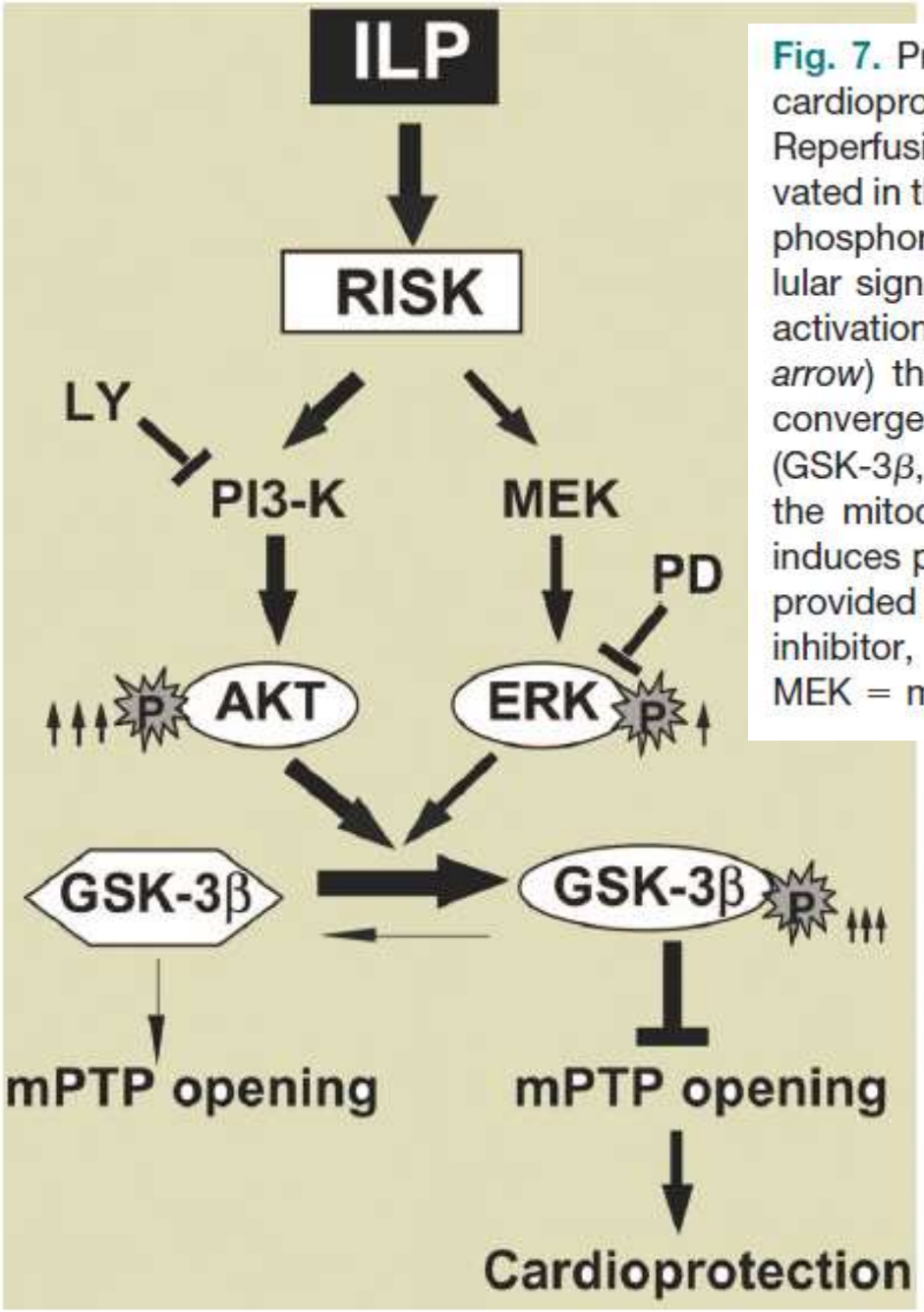


Fig. 7. Proposed mechanisms underlying Intralipid-induced cardioprotection against ischemia/reperfusion injury. The Reperfusion Injury Salvage Kinases (RISK) pathway is activated in the presence of Intralipid (ILP), resulting in increased phosphorylation of both protein kinase B (Akt) and extracellular signal-regulating kinase (ERK), although the degree of activation is much more prounnced in Akt (eightfold, *thick arrow*) than in ERK (threefold, *thin arrow*). Both pathways converge to phosphorylate glycogen synthase kinase-3β (GSK-3β, inactive form), which in turn inhibits the opening of the mitochondrial permeability transition core (mPTP) and induces protection against reperfusion injury. The protection provided by Intralipid is fully abolished by the PI3K-specific inhibitor, LY294002 (LY), and partially by PD98059 (PD). MEK = mitogen-activated protein kinases kinase.

Conclusions

We show here that only one bolus of Intralipid (20%) right before reperfusion is sufficient to protect the heart against ischemia/reperfusion injury *in vivo*. Intralipid application at the reperfusion also improves the functional recovery of isolated Langendorff-perfused mouse hearts approximately fourfold and significantly reduces the infarct size. Postischemic administration of Intralipid inhibits the opening of the mPTP. Phosphorylation of GSK-3β, which has emerged as a new target for cardioprotection, is involved in the cardioprotective action of Intralipid against ischemia/reperfusion injury. Intralipid has already been in clinical use for almost four decades for patients who need total parenteral nutrition, and it has been shown to be safe and well tolerated. Here we propose that Intralipid could be a clinically safe compound for targeting GSK-3β at the time of reperfusion to protect the myocardium against ischemia/reperfusion injury and certainly warrant further investigation in human heart.

Treatment of poisoning caused by β-adrenergic and calcium-channel blockers

GREENE SHEPHERD

Purpose. The toxic effects and treatment of β-adrenergic blocker and calcium-channel blocker (CCB) overdose are reviewed.

Purpose. The toxic effects and treatment of β-adrenergic blocker and calcium-channel blocker (CCB) overdose are reviewed.

Summary. Overdoses with cardiovascular drugs are associated with significant morbidity and mortality. Beta-blockers and CCBs represent the most important classes of cardiovascular drugs. In overdose, β-blockers and CCBs have similar presentation and treatment overlaps and are often refractory to standard resuscitation measures. The common feature of β-blocker toxicity is excessive blockade of the β-receptors resulting in bradycardia and hypotension. Poisoning by CCBs is characterized by cardiovascular toxicity with hypotension and conduction disturbances, including sinus bradycardia and varying degrees of atrioventricular block. Therapies include β-agonists, glucagon, and phosphodiesterase inhibitors. However, in β-blocker poisoning where symptomatic bradycardia and hypotension are present, high-dose glucagon is considered the first-line antidote. Traditionally, antidotes for CCB overdose have included calcium, glucagon, adrenergic drugs, and amrinone. For cases of CCB poisoning where cardiotoxicity is evident, first-line therapy is a combination of calcium and epinephrine; high-dose insulin with supplemental dextrose and potassium therapy (HDIDK) is reserved for refractory cases. Health-system pharmacists should be aware that when these drugs are used as antidotes, higher than normal dosing is needed.

Conclusion. Poisoning by β-blockers or CCBs usually produces hypotension and bradycardia, which may be refractory to standard resuscitation measures. For cases of β-blocker poisoning where symptomatic bradycardia and hypotension are present, high-dose glucagon is considered the first-line antidote. For cases of CCB poisoning where cardiotoxicity is evident, a combination of calcium and epinephrine should be used initially, reserving HDIDK for refractory cases.

Index terms: Amrinone; Antidotes; Calcium; Calcium antagonists; Combined therapy; Dextrose; Dosage; Epinephrine; Glucagon; Insulin; Phosphodiesterase inhibitors; Poisoning; Potassium; Sympatholytic agents; Sympathomimetic agents; Toxicity

Am J Health-Syst Pharm. 2006; 63:1828-35

Table 1.
Comparison of Pharmacologic Properties of Various β-Blockers[a]

Agent	Adrenergic Receptor Blocking Activity	Lipid Solubility	Intrinsic Sympathomimetic Activity	Sodium Channel Blocking
Acebutolol	β_1	Low	Yes	Yes
Atenolol	β_1	Low	No	No
Betaxolol	β_1	Low	No	Yes
Bisoprolol	β_1	Low	No	No
Carteolol	β_1, β_2	Low	Yes	No
Carvedilol	$\alpha_1, \beta_1, \beta_2$	High	No	No
Esmolol	β_1	Low	No	No
Labetalol	$\alpha_1, \beta_1, \beta_2$	Moderate	Yes	No
Metoprolol	β_1	Moderate	No	No
Nadolol	β_1, β_2	Low	No	No
Oxprenolol	β_1, β_2	High	Yes	Yes
Penbutolol	β_1, β_2	High	Yes	No
Pindolol	β_1, β_2	Moderate	Yes	No
Propranolol	β_1, β_2	High	No	Yes
Sotalol	β_1, β_2	Low	No	No
Timolol	β_1, β_2	Low to moderate	No	No

[a]Adapted with permission from reference 5.

Table 2.

Threshold and Toxic Oral Doses of Common β-Adrenergic Blockers[a]

Drug and Patient Age	Threshold Dose for Referral[b]	Lowest Reported Toxic Dose
Acebutolol hydrochloride[c]		
Adult	600 mg	4000 mg
Child	12 mg/kg	NC
Atenolol		
Adult	200 mg	500 mg
Child	2 mg/kg	5.3 mg/kg
Carvedilol		
Adult	50 mg	1050 mg
Child	0.5 mg/kg	NC
Labetalol hydrochloride		
Adult	400 mg	6000 mg
Child	20 mg/kg	NC
Metoprolol succinate (ER)		
Adult	400 mg	7500 mg[d]
Child	5 mg/kg	NC
Metoprolol tartrate (IR)		
Adult	450 mg	7500 mg[d]
Child	2.5 mg/kg	NC
Nadolol		
Adult	320 mg	NC
Child	2.5 mg/kg	NC
Propranolol hydrochloride		
Adult	240 mg	800 mg
Child		
IR	4 mg/kg	5 mg/kg
ER	5 mg/kg	12 mg/kg
Sotalol hydrochloride		
Adult	160 mg	560 mg
Child	4 mg/kg	NC
Timolol maleate		
Adult	30 mg	NC
Child	Any dose	NC

[a]Adapted, with permission, from reference 7. Doses are based on the assumption that ingestion was unintentional in an asymptomatic patient without underlying severe medical conditions or concomitant ingestion of calcium-channel blockers. NC = no case reports available, ER = extended-release formulation, IR = immediate-release formulation.

[b]Dose during acute ingestion that should prompt referral to a hospital.

[c]Doses expressed in terms of the drug base.

[d]Dose expressed in terms of metoprolol tartrate equivalents.

Table 3.
Threshold and Toxic Oral Doses of Common Calcium-Channel Blockers[a]

Drug and Patient Age	Threshold Dose for Referral[b]	Lowest Reported Toxic Dose
Amlodipine besylate[c]		
Adult	10 mg	30 mg
Child	0.3 mg/kg	0.4 mg/kg
Bepridil hydrochloride		
Adult	300 mg	NC
Child	Any dose	NC
Diltiazem hydrochloride		
Adult		
IR	120 mg	360 mg
12-hr ER	360 mg	700 mg
24-hr ER	540 mg	NC
Child	1 mg/kg	180 mg[d]
Felodipine		
Adult	10 mg	NC
Child	0.3 mg/kg	NC
Isradipine		
Adult	20 mg	NC
Child	0.1 mg/kg	2.5 mg/kg
Nicardipine hydrochloride		
Adult		
IR	40 mg	260 mg
ER	60 mg	600 mg
Child	20 mg	1.25 mg/kg
Nifedipine		
Adult		
IR	30 mg	50 mg
ER	120 mg	200 mg
Child	Any dose	2.8 mg/kg
Nimodipine		
Adult	60 mg	NC
Child	Any dose	NC
Nisoldipine		
Adult	30 mg	NC
Child	Any dose	NC
Verapamil hydrochloride		
Adult		
IR	120 mg	160 mg
ER	480 mg	720 mg
Child	2.5 mg/kg	12 mg/kg

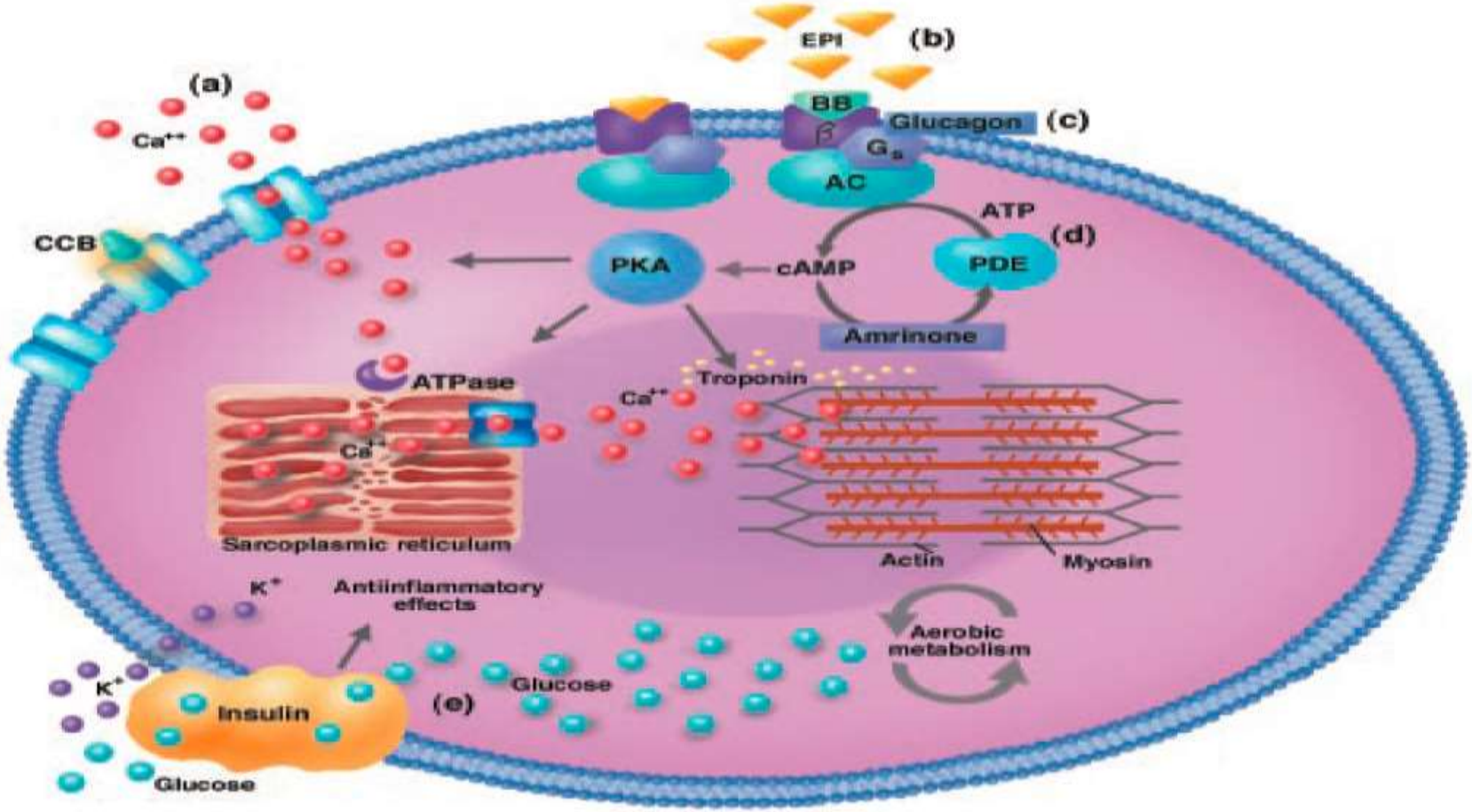
[a]Adapted, with permission, from reference 8. Doses are based on the assumption that ingestion was unintentional in an asymptomatic patient without underlying severe medical conditions or concomitant β-adrenergic blockers. NC = no case reports available, IR = immediate-release formulation, ER = extended-release formulation.

[b]Dose during acute ingestion that should prompt referral to a hospital.

[c]Doses expressed in terms of the drug base.

[d]Formulation unknown.

Figure 1. Proposed actions in cardiac muscle of calcium, epinephrine (EPI), glucagon, amrinone, and insulin in the treatment of β-blocker (BB) and calcium-channel blocker (CCB) toxicity: (a) Calcium enters open voltage-sensitive calcium channels to promote the release of calcium from the sarcoplasmic reticulum. The released calcium combines with troponin to cause muscle contraction via actin and myosin fibers. (b) EPI binds to β-receptors (β) that are not occupied by a BB. Stimulation of the receptors, which are coupled to a G protein (G_s), brings about the activation of adenylate cyclase (AC). AC catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA), which promotes the opening of dormant calcium channels, enhances release of calcium from the sarcoplasmic reticulum, and facilitates release of calcium by troponin during diastole. Therapies that promote cAMP formation generally have transient effects in CCB overdose due to the myocyte running out of carbohydrates. (c) Glucagon bypasses β-receptors and acts directly on G_s to stimulate conversion of ATP to cAMP. (d) Amrinone inhibits phosphodiesterase (PDE) to prevent the degradation of cAMP. (e) Insulin promotes the uptake and use of carbohydrates as an energy source. It also promotes antiinflammatory effects that may correct problems caused by inefficient energy production. The associated influx of potassium may also provide benefit by prolonging repolarization and allowing calcium channels to remain open longer. Illustration by Marie Dauenheimer, CMI. Adapted, with permission, from reference 16.



Conclusion

Poisoning by β-blockers or CCBs usually produces hypotension and bradycardia, which may be refractory to standard resuscitation measures. For cases of β-blocker poisoning where symptomatic bradycardia and hypotension are present, high-dose glucagon is considered the first-line antidote. For cases of CCB poisoning where cardiotoxicity is evident, a combination of calcium and epinephrine should be used initially, reserving HDIDK for refractory cases.

EDUCATION

Bruno Riou, M.D., Ph.D., Editor

Case Scenario: Opioid Association with Serotonin Syndrome

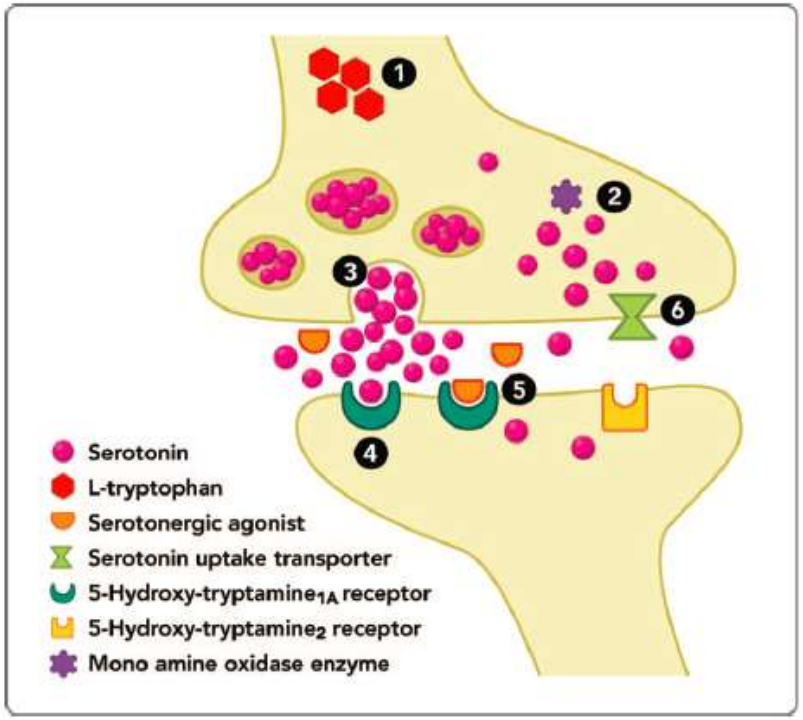
Implications to the Practitioners

Rahul Rastogi, M.B.B.S.,* Robert A. Swarm, M.D.,† Trusharth A. Patel, M.D.‡

 Anesthesiology 2011; 115:1291–8

Table 1. Timeline of Development of Symptoms and Management in Case Two

Time	Health Care Visits	Management
Day 0	Inadequate pain control.	Increase frequency of fentanyl patch replacement to every 48 h.
Day 7	Outpatient visit: Anxiety, tremulous, fever, and sweating.	Diagnosed as anxiety, started on 0.2 mg oral clonidine every 4 h.
Day 8	(24 h later) Persistence of symptoms.	Self-discontinuation of fentanyl patch.
Day 9	(12–14 h later) Emergency room visit 1: additional symptom of mild confusion.	Treated with 5 mg haloperidol and 2 mg lorazepam for agitation and anxiety, and discharged home.
Day 9	(Within 12 h) Emergency room visit 2: additional symptoms of yawning and insomnia.	Urine drug screen negative for opiates; diagnosed as acute opioid withdrawal; treated with fentanyl patch reapplication (after no fentanyl for 30–32 h); and admitted to hospital.
Day 10	(Within 8 h) Pain consult: diagnosis of serotonin syndrome made.	Treated with discontinuation of fentanyl (within 8 h of reapplication), oxycodone, citalopram and mirtazapine. Supplement with intravenous morphine sulphate as needed.
Day 11	Complete resolution of symptoms, vitals stabilized.	Restarted 45 mg morphine sulphate extended release tablet twice a day and 15 mg instant release tablet every 6 h as needed; restarted citalopram and mirtazapine.



1 Increased synthesis
i.e. increase substrate: L-tryptophan

2 Decreased metabolism
Monoamine oxidase inhibitors (MAOIs):
Phenelzine, Tranylcypromine, Moclobemide, Selegiline, Isocarboxazid, Linezolid, Methylene blue

3 Increased release:
Amphetamines, Cocaine, Fenfluramine, Sibutramine, Ecstasy, Phenantherene Opioids (Oxycodone, buprenorphine), Tramadol

4 Serotonin (5-hydroxy-tryptamine) receptor agonism:
Buspirone, Lysergic acid diethylamide (LSD), Di-hydro ergotamine (DHE), Triptans, Mirtazapine

5 Increased serotonin (5-hydroxy-tryptamine) receptor sensitivity:
Lithium

6 Decreased reuptake:
Tricyclic Antidepressants (TCAs):
Amitriptyline, Imipramine, Clomipramine, Desipramine, Doxepin

Selective serotonin reuptake inhibitors (SSRIs):
Paroxetine, Sertraline, Fluoxetine, Fluvoxamine, Citalopram, Escitalopram

Serotonin noradrenaline reuptake inhibitors (SNRIs):
Venlafaxine, Duloxetine, Milnacipran

Other Antidepressants:
Trazodone, Nefazodone

Opioids:
Fentanyl, Methadone, Meperidine, Dextromethorphan, Tramadol

Miscellaneous:
Ondansetron, Granisetron, St. John's Wort

Fig. 1. Increase intrasynaptic serotonin levels: Mechanisms and associated serotonergic agents.

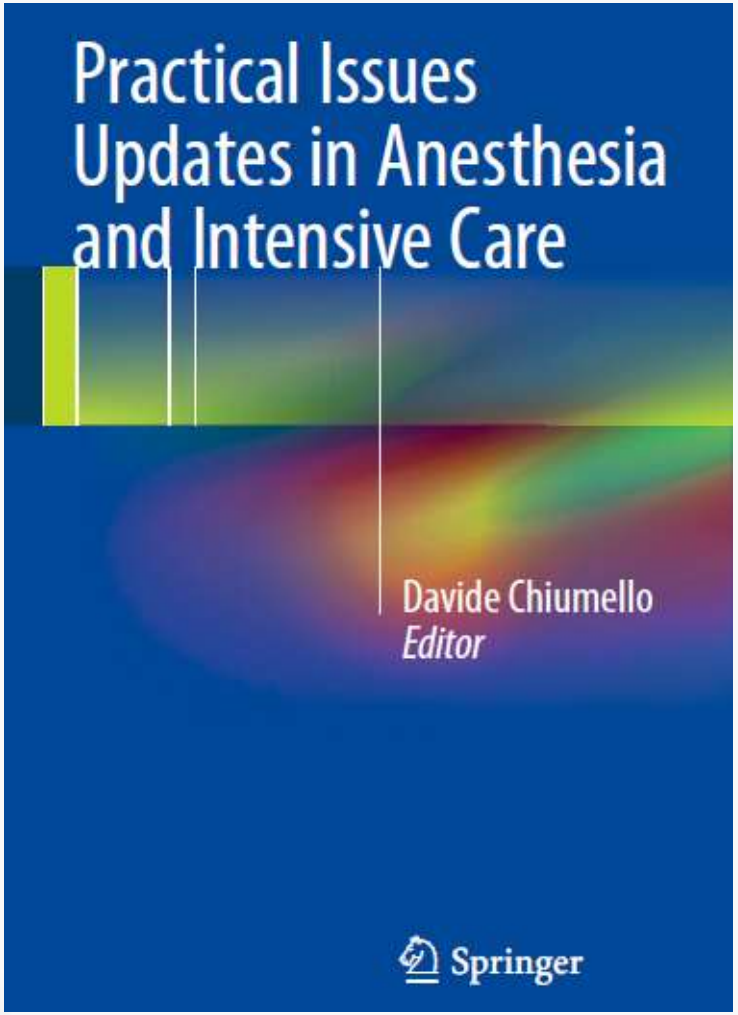
Fig. 2. Spectrum of serotonin syndrome and their management strategies.

Table 3. Diagnostic Criteria for Serotonin Syndrome

Sternbach's Criteria	Hunter Serotonin Toxicity Criteria
A. Recent addition or increase of serotonergic agent	History of serotonergic agent usage
B. No recent addition or increase of neuroleptic agent	
C. Rule out other etiologies, such as infections, substance abuse or withdrawal	
At least three of the following: 1. Altered mental status (confusion, hypomania) 2. Agitation 3. Myoclonus 4. Hyperreflexia 5. Diaphoresis 6. Shivering 7. Tremor 8. Diarrhea 9. Poor coordination 10. Fever	At least one or more of following: 1. Clonus: spontaneous, inducible, ocular 2. Agitation 3. Autonomic dysfunction (*i.e.* hyperthermia) 4. Tremor 5. Hyperreflexia

Table 4. Differential Diagnosis of Serotonin Syndrome

Clinical Conditions	Distinguishing Features
Serotonin syndrome (serotonin excess)	Cognitive: anxiety, agitation, confusion, hypomania, visual hallucinations, restlessness, disorientation, and coma. Autonomic: hyper/hypotension, tachycardia, tachypnea, diarrhea, mydriasis, diaphoresis, and hyperthermia. Neuromuscular: muscle rigidity, tremors, nystagmus, myoclonus, ocular clonus, hyperreflexia, ataxia, and trismus
Neuroleptic malignant syndrome (dopamine antagonism)	Extrapyramidal symptoms, "lead pipe" rigidity, gradual onset, bradykinesia, absence of gastrointestinal hyperactivity, myoclonus, and hyperreflexia
Anticholinergic syndrome (cholinergic antagonism)	History of anticholinergic agent use (such as tricyclic antidepressants), widened pulse pressure, dry skin and mucus membranes, normal reflexes, absence of myoclonus, and gastrointestinal hyperactivity
Malignant hyperthermia	History of halogenated anesthetic and depolarizing muscle relaxant exposure, hyporeflexia, and absence of myoclonus
Opioid toxicity	History of opioid exposure, miosis, hypotension, hypothermia, bradycardia, hypopnea, and hyporeflexia
Opioid withdrawal	History of sudden opioid discontinuation or intake of opioid antagonist agents, piloerection, joint pains, "flu-like" symptoms, absence of hyperreflexia, and myoclonus



12

All You Need to Know About the Meaning of Plasmatic Lactate Level

L. di Girolamo, R. Iorio, G. Spinelli, and M. Dei Poli

Table 12.1 (continued)

Cause	Presumed mechanism or mechanisms	Comments
Metformin	Interference with oxidative phosphorylation, suppression of hepatic gluconeogenesis	This is usually seen in association with high plasma metformin levels; treatment with dialysis is beneficial
Nucleoside reverse-transcriptase inhibitors	Interference with oxidative phosphorylation	Marked hyperlactatemia is uncommon in the absence of other predisposing factors
Cocaine	Decreased O_2 delivery to tissues and epinephrine-induced β2-adrenoceptor stimulation	Marked hyperlactatemia is seen in some patients having seizures or being restrained
Toxic alcohols, methanol, ethylene glycol, diethylene glycol	Interference with oxidative phosphorylation	The increase in lactate is small; a small increase in the osmolal gap (usually <20 mOsm/kg H_2O) can be seen in some cases of lactic acidosis without toxic alcohols
Propylene glycol	d-Lactate and l-lactate are normal products of metabolism	Lactic acidosis can occur in the absence of impaired oxidative phosphorylation
Salicylates	Interference with oxidative phosphorylation	Hyperlactatemia is usually minimal
Cyanide	Interference with oxidative phosphorylation	Lactic acidosis is an important manifestation of poisoning
β2-Agonists	Stimulation of aerobic glycolysis	This is most common with treatment of acute asthma; hypokalemia can result from enhanced cellular uptake of potassium
Propofol	Interference with oxidative phosphorylation	Lactic acidosis can be seen with prolonged high-dose infusion
Thiamine deficiency	Impairment of pyruvate-dehydrogenase activity	This is most common in children or adults receiving parenteral nutrition or those with fulminant beriberi

Data from Indellinger [18]
PaO2 denotes partial pressure of arterial oxygen

Nuove terapie

- Infusione lipidi
- Glucosio-insulina ad alte dosi
- (0,5-1 UI/kg /ora)
- Dexmedetomidina
- Dantrolene 1 mg / Kg ogni 6 ore