Inside this issue:

ANTIVENOM

HOSPITAL SEGAMAT

Pharmacy Bulletin
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Brief historical perspective

Antivenom was first developed as a specific antidote to treat snakebite in the late 1890's by two major independent groups. Albert Calmette appears to have been the first successfully to develop and deploy an antivenom, for treatment of cobra envenoming. Both he and others, including Vital Brazil in Sao Paulo, Brazil used horses immunized with venom as a source of neutralizing IgG antibodies.

A number of countries with perceived snakebite problems, including Australia, Brazil and South Africa embarked on programmes to develop antivenoms to treat bites by local snakes, so that by the 1950's, a wide variety of equine antivenoms were in production. With few exceptions, these antivenoms remain in production today, with little variation in production technique and only rarely have they been tested for efficacy in controlled trials.

The only antivenoms to have been subjected to modern trial methods proving efficacy and safety are generally those developed recently or older products used as a standard against which the new products have been measured. It has generally been accepted as fact that antivenoms for snakebite work.

At the start of the 21st century we find ourselves facing a world with a contracting diversity and supply of antivenoms, despite growing evidence that in many regions, the frequency and distribution of venomous snakes and snakebite are increasing

Indication of Antivenom Treatment

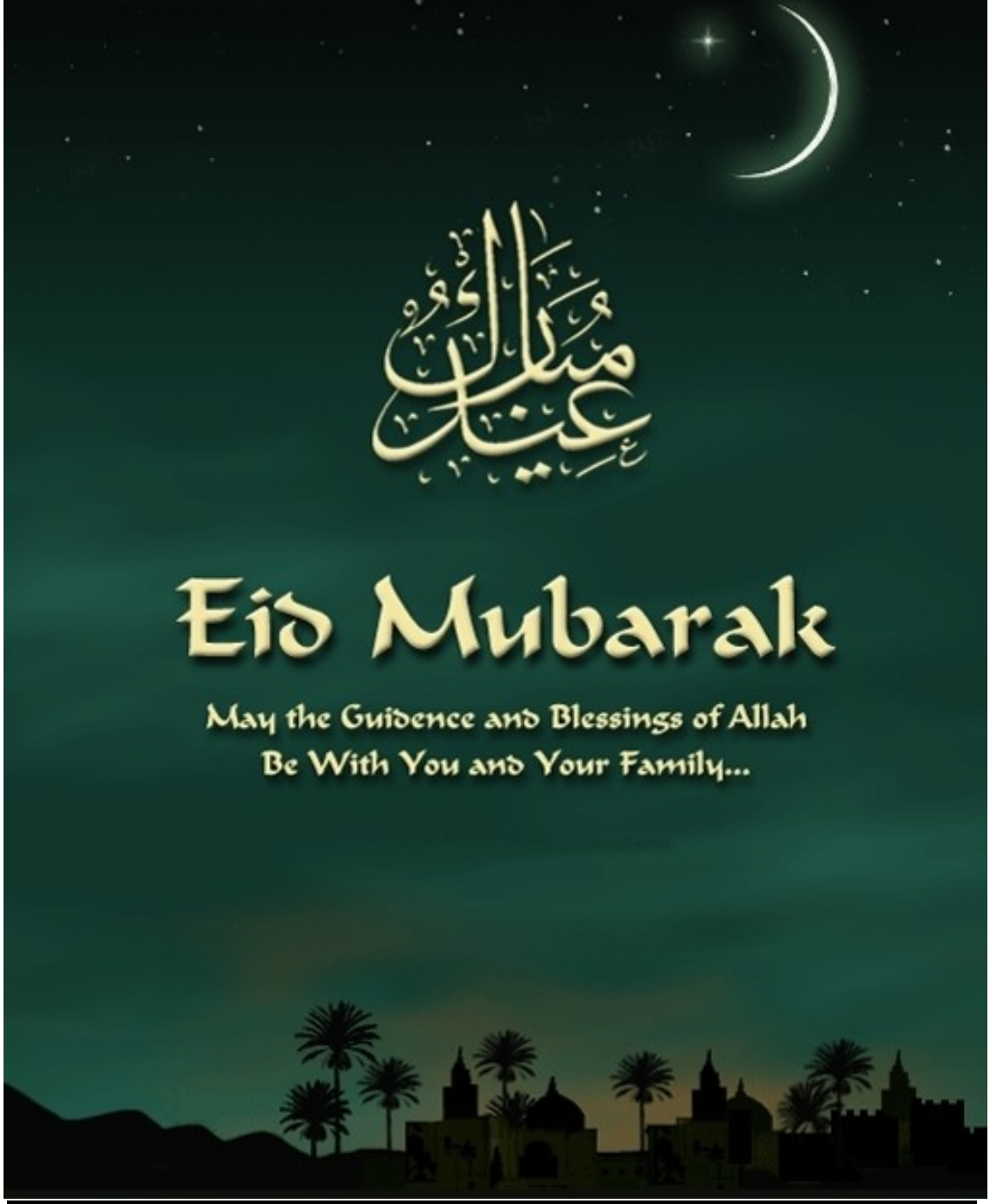
Antivenom is selected **ONLY** if its stated range of specificity and para-specific neutralization capacity includes the species known or highly suspected to have been responsible for the bite. Antivenom treatment is recommended when a patient with proven or suspected snake-bite develops one or more of the following signs

Systemic envenoming

1. Haemostatic abnormalities: Spontaneous systemic bleeding, coagulopathy (20WBCT or other laboratory tests) or thrombocytopenia (<100 x 10^9/l).
2. Neurotoxic signs: ptosis, external ophthalmoplegia, paralysis etc.
3. Cardiovascular abnormalities: hypotension, shock, cardiac arrhyth-
4. Acute kidney injury (renal failure): oliguria/anuria, rising blood creatinine/urea.
5. Haemoglobin-/myoglobinuria (dark brown/black urine).
6. Other evidence of intravascular haemolysis or generalized rhabdomyolysis (muscle aches and pains, hyperkalaemia, rapidly raising Creatine Kinase/CPK level).

Local envenoming (requires other considerations)

1. Local painful swelling involving more than half of the bitten limb (in the absence of a tourniquet) within 48 hours of the bite.
2. Rapid extension of swelling (for example, beyond the wrist or ankle within a few hours of bite on the hands or feet) or significant swelling after bites on the digits (toes and especially fingers).
3. Development of enlarged tender lymph nodes draining the bitten limb.



Wishing all the best to; Nur Raihanah A Rahman, Nur Syafiqah Anuar, Fairuz Fakharudin, Mohd Samsul Arif, Syafuad Yahya

Welcoming new PRP : Zulaika, YanZhuang, Anisah Fathin, Munirah and Linda

TDM SERUM SAMPLING GUIDE (cont'd)

DRUG	STEADY STATE	SAMPLING TIME	SAMPLE STABILITY
LITHIUM	4-5 days	Pre: 12 hours after dose (BD)	-
PARACETAMOL	Toxicity: 4 hours after ingestion	Toxicity: 4 hours after single acute ingestion OR Unknown ingestion time: 2	8 hours
PHENOBARBITAL	Without LD: 2-3 weeks After LD: 2-3 hours	Pre: 0-30 min before dose	8 hours
PHENYTOIN	With LD: 12-24 hours	Pre: 0-30 min before dose	8 hours
SALICYCLATE	Therapeutic: 5-7 days Toxicity: 4 hours after ingestion	Therapeutic: 1-3 hours after dose Toxicity: 4 hours after ingestion	8 hours
TACROLIMUS	3-5 days	Pre: 0-30 min before dose	-
THEOPHYLLINE / AMINOPHYLLINE	Adults: 2 days Children: 1-2 days Infants: 1-5 days Newborn: 5 days Premaure neonates: 6	Pre: 0-30 min before dose	8 hours
VALPROIC	2-4 days	Pre: 0-30 min before dose	2 days
VANCOMYCIN	Normal renal function: After 3rd dose Impaired renal function: After 1st stat dose	Trough level: 30 mins before dose Peak level: 1 hour after the infusion completed	4 hours

SDD: Single daily dosing MDD: Multiple daily dosing LD: Loading dose MD: Main-

References:i) Martindale 33th Ed 2002 ii) Basic Clinical Pharmacokinetic (Winter) 2004 iii) Drug Information Handbook 10th Ed 2003 iv) British National Formulary, Vol 50 Sept 2005 v) Micromedex ® Healthcare Series Vol 130 2006 vi) Infectious Disease Society of America vii) Drug Doses, Frank Shann 16th Ed 2014

DOSE OF ANTIVENOM

In practice, the choice of an initial dose of antivenom is usually empirical (based on clinical presentation) or based on manufacturer's recommendation. Children are given exactly the same dose of antivenom as adults but at a lower dilution ratio (volume).

ANTIVENOM ADMINISTRATION

Choice of antivenom must be selected by a physician or clinical toxinologist who is familiar and experienced with snakebite management in Malaysia. All antivenom is administered intravenously.

1 The snake species is identified (use monovalent/mono-specific antivenom)

2 The snake species is unidentified (use Neuro-polyvalent or Hemato-polyvalent antivenom)

3 Adrenaline drawn up in readiness before antivenom is administered (IM 0.5 mg for adults and IM 0.01mg/kg body weight for children (0.1% solutions, 1 in 1,000 dilution, 1mg/ml).

4 Method: Intravenous infusion. Reconstitute freeze-dried antivenom with the solution supplied or 10ml WFI. Gently swirl (never shake) to dissolve the freeze-dried antivenom. Further dilute with 5-10ml of NS or D5% per kg body weight for children or 250-500ml NS or D5% for adult). Infused the antivenom mixture starting slow (1 to 2 ml/min) over 10-15 min then increased to a higher rate if no reaction to complete within a period of one hour or earlier.

5 Closely observe patient during and for at least one hour AFTER completion of intravenous infusion. Serially chart vital signs and clinical progression.

√	GUIDE TO ANTIVENOM APPROPRIATE FOR MALAYSIA Species	Antivenom manufacturer	First Dose/vials
	Monocle cobra,	QSMI Thai Red Cross: Cobra Antivenin to neutralize 0.6 mg/ml of venom	100mls/10 vials Subsequent dose 1-2 hr
	King Cobra, *Ophiophagus hannah*	QSMI Thai Red Cross: King Cobra Antivenin to Neutralize 0.8 mg/ml of venom	100mls/10 vials Subsequent dose 1-2 hr
	Malayan krait, *Bungarus candidus*	QSMI Thai Red Cross: Malayan Krait Antivenin to Neutralize 0.4 mg/ml of venom	50mls/5 vials Subsequent dose 1-2 hr
	Banded krait, *Bungarus fasciatus*	QSMI Thai Red Cross: Banded Krait Antivenin to Neutralize 0.6 mg/ml of venom	50mls/5 vials Subsequent dose 1-2 hr
	Malayan pit viper, *Calloselasma Rhodostoma*	QSMI Thai Red Cross: Malayan Pit Viper Antivenin to Neutralize 1.6 mg/ml of venom	30mls/3 vials Subsequent dose 6 hr
	Green pit viper, *Cryptelytrops Albolabris*	QSMI Thai Red Cross: Green Pit Viper Antivenin to Neutralize 0.7 mg/ml of venom	30mls/3 vials Subsequent dose 6 hr
	Malayan pit viper, *Calloselasma rhodostoma*, Green pit viper, *Cryptelytrops Albolabris*, SEA Russell's Viper, *Daboia russelli siamensis*	QSMI Thai Red Cross: Hemato Polyvalent Snake Antivenom	30mls/3 vials Subsequent dose 6 hr
	Monocled Cobra, *Naja kaouthia*, King Cobra *Ophiophagus hannah*, Banded Krait *Bungarus fasciatus*, Malayan Krait, *Bungarus candidus*.	QSMI Thai Red Cross: Neuro Polyvalent Snake Antivenom	50-100mls/ 5-10 vials Subsequent dose 1-2 hr
	Sea snakes, *Hydrophiidae* family.	CSL, Australia: Polyvalent Sea snake Antivenom	10-30mls/1-3 vials Subsequent dose 1-2 hr

Note: Subsequent doses are according to the clinical symptoms. Monocle cobra, *Naja kaouthia* antivenom has good cross neutralization with the Equatorial spitting cobra, *Naja sumatrana* venom. Malayan pit viper, *Calloselasma rhodostoma*, SEA Russell's Viper, *Daboia siamensis* and Monocle cobra, *Naja kaouthia* are not indigenous to Borneo. The VINS Indian Polyvalent antivenom is not appropriate for treating pit viper envenomations in Malaysia. It may have limited neutralizing capacity against the venoms of Equatorial spitting cobra, *Naja sumatrana*, Monocle cobra, *Naja kaouthia*, King Cobra, *Ophiophagus Hannah* and Malayan Krait, *Bungarus candidus*. However its use is not recommended in Malaysia or SEA region.

(Snakebite Management Guide For Healthcare Providers In Malaysia – updated August 2015)

THERAPEUTIC DRUG MONITORING

Assays that will be ran in Hospital Segamat

1) Acetominophen
2) Carbamazepine
3) Digoxin
4) Gentamicin
5) Phenobarbitone
6) Phenytoin
7) Sodium Valproate
8) Theophylline / Aminophylline
9) Vancomycin

Assays that will be outsourced to other facilities

1) Amikacin
2) Cyclosporin
3) Lithium
4) Salicylate
5) Tacrolimus

TDM SERUM SAMPLING GUIDE

DRUG		STEADY STATE		SAMPLING TIME		SAMPLE STABIL-
AMINOGLYCOSIDE	AMIKACIN	SDD	MDD	SDD	MDD	-
		Adult & Paed After 2nd dose	Adult Pre & Post 4th dose Paed Pre & Post 3rd dose	1st sample Post 2 hours 2nd sample post 6 hours	Pre 0-30 min before dose Post 60 min after 60 min infusion completed	8 hours
	GENTAMICIN	IP: before 3rd bag		IP: pre (0-30 min before dose)		4 hours
CAR-BAMAZEPIN		Initiation: 2-3 weeks MD: 2-5 days after initia-		Pre: 0-30 min before dose		8 hours
CYC-LOSPORINE		3-5 days		C0: Immediately before next dose		8 hours
DIGOXIN		Withold LD: 7-14 days With LD: 12-24 hours ESRD: 15-20 days		Pre: 0-30 min before dose OR Post: Oral: at least 6 hours after dose		8 hours

MADRAC
Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia

PARACETAMOL: RISK OF SERIOUS SKIN REACTIONS

The commonly used analgesic/ antipyretic medication, paracetamol (also known as acetaminophen), has been associated with a risk of rare but serious skin reactions, namely Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP).

The NPCB performed a review on this matter following a drug safety communication issued by the US FDA regarding this risk. The US FDA review of their adverse event reporting system database revealed 107 reports of serious skin reactions, the majority involving single-active ingredient paracetamol products. In the medical literature, there were three (3) case reports involving positive rechallenge, where the patients had a recurrence of serious skin reactions when given paracetamol again.

Local Scenario

In Malaysia, there are currently 268 products containing paracetamol registered with the DCA, including 65 combination products. In general, products containing paracetamol are approved for the treatment of mild pain or fever. Some combination products are also indicated for the relief of cold and flu symptoms.

From year 2000 to Feb 2015, the NPCB has received **1,018 ADR reports** related to paracetamol, with 1,972 adverse events. A total of 790 reports (78%) involved at least one skin reaction, with the most commonly reported ADRs being pruritus, rash, urticaria, and angioedema. There

Advice to Health-care Professionals:

- Advise patients to **stop taking** paracetamol and seek medical advice at the **first signs of serious skin reactions**, including fever, sore throat, skin reddening, eye irritation, blisters or rash.
- Patients who have experienced a serious skin reaction with paracetamol should be counselled not to take the drug again and must be provided with an **allergy card or medical alert tag.**
- Please **report** any suspected ADR related to paracetamol use to the NPCB, including situations where several drugs are given concomitantly.

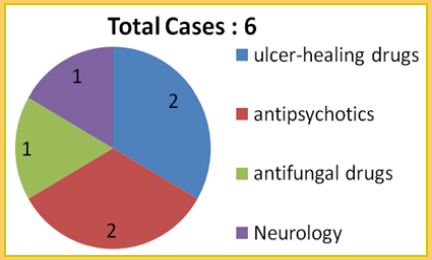
were a total of **30 reports** involving **serious skin reactions**, namely SJS

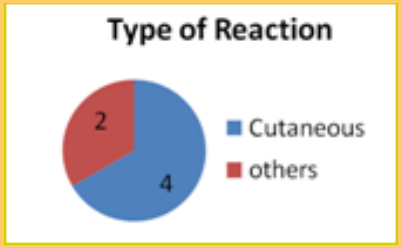
(18 reports), erythema multiforme (5), TEN (4), SJS-TEN overlap (2), and AGEP (1). The time to onset of reaction for these cases ranged from 24 hours (recurrence on second exposure) to several days.

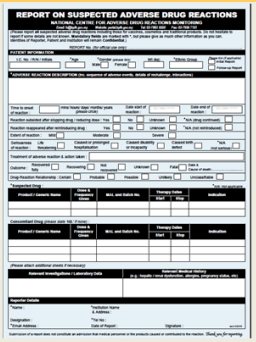
On 3 June 2015, the DCA issued a directive *[Bil. (29) dlm. BPFK/PPP/07/25]* requiring all product registration holders of paracetamol-containing products to update their local product information (including labels, package inserts, and consumer medication information leaflets – RiMUPs) with a warning on the risk of serious skin reactions.

(Malaysia Adverse Drug Reactions Newsletter August 2015)

ADR Cases in Hospital Segamat January to June 2016







New ADR Form is available in Pharmacy Department

Or

Download from National Pharmaceutical Regulatory Agency http://npra.moh.gov.my/