Toxicity of cyanides given by intramuscular injection

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Lethal intramuscular injections of hydrogen cyanide (HCN) do not produce specific macroscopical or histological features, the only positive finding being inhibition of cytochrome oxidase in central nervous tissue (Ballantyne, 1970). Because of the forensic importance of detecting cyanide after parenteral administration, we investigated the toxicology of HCN and KCN given by intramuscular injection to rabbits. Tissue and blood cyanide levels were measured by a modified Epstein (1947) technique (Ballantyne, Bright & Williams, 1970).

The acute intramuscular LD50 values for HCN and KCN differ significantly when expressed as a whole molecule, but calculated as the cyanide radical the only significant difference is a lower LD50 for HCN in females (Table 1). Rabbits given HCN die more quickly (Table 1) and have higher blood cyanide levels (Table 2).

TABLE 1. *Comparison of LD50 values and times to death for adult rabbits given intramuscular HCN or KCN*

	LD50 with 95% confidence limits (mg/kg)			
	HCN		KCN	
Sex	as HCN	as cyanide radical	as KCN	as cyanide radical
Male	1·50 (1·27–1·80)	1·45 (1·22–1·73)	3·06 (2·61–3·63)	1·23 (1·05–1·45)
Female	0·95 (0·81–1·11)	0·91 (0·78–1·07)	3·27 (2·70–4·08)	1·31 (1·08–1·63)

	Times to death as mean±S.E.	
	HCN	KCN
Male	266±21	603±50
Female	395±59	436±19

TABLE 2. *Concentrations of cyanide, expressed as mean±S.E., in blood and various normal (blood-containing) or saline perfused tissues from female rabbits killed by intramuscular HCN or KCN at a dose of 8 mg CN/kg (six animals in each group)*

	Cyanide concentration*					
	HCN			KCN		
Tissue	Normal	Perfused	*P*†	Normal	Perfused	*P*†
Skeletal muscle	35·0±5·2	9·3±2·7	<0·001	29·6±2·4	7·8±2·4	<0·001
Kidney	74·7±10·3	11·0±4·3	<0·001	52·0±11·0	2·3±1·1	<0·005
Liver	148·7±32·3	43·7±13·5	<0·02	82·0±7·9	6·5±0·8	<0·001
Spinal cord	48·5±4·9	49·8±14·7	>0·9	36·8±3·5	22·5±3·8	<0·05
Brain	145·3±37·2	289·0±67·7	0·1	106·5±12·4	98·0±5·0	<0·6
Whole blood	690±80	760±130	<0·7	450±34	438±8	<0·7
Serum	280±18	260±48	<0·8	161±21	134±8	<0·3

* Concentrations expressed as μg CN/100 g wet tissue and 100 ml blood or serum; † significance of difference between normal and perfused tissues.

Cyanide estimations (Table 2) demonstrate higher concentrations in whole blood than in serum. The comparative blood and tissue cyanide concentrations are higher in animals killed with HCN. Estimations on saline perfused tissues demonstrate that most of the activity in muscle, kidney and liver is due to their blood content, but a selective concentration occurs in central nervous tissue.

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Jumping after naloxone precipitated withdrawal of chronic morphine in the rat

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There have been several reports (Maggiolo & Huidobro, 1961; Way, Loh & Shen, 1968; Marshall & Weinstock, 1969) that mice can be made physically dependent on morphine-like drugs and that one of the withdrawal effects after challenge with a morphine antagonist is jumping. Although Buckett (1964) and Lorenzetti & Sancilio (1970) have described morphine withdrawal effects in rats, jumping was not reported.

We have been able to produce and quantitate morphine withdrawal jumping in the rat similar to the effect in mice recently demonstrated to the Society by Marshall (1970).

Male Wistar albino rats weighing 100–120 g were given subcutaneous injections of morphine sulphate at 0.900 h, 12.00 and 16.00 h for 4 days and at 0.900 h on the fifth day. The dose of morphine was raised gradually from an initial 10·0 mg base/kg to a final 33·6 mg base/kg. Naloxone hydrobromide at 0·25 mg base/kg was given subcutaneously 5 h later to precipitate withdrawal effects.

Immediately after naloxone challenge, each rat was placed in a plastic bucket 25 cm high, covered by a perforated transparent lid. The rats showed typical morphine withdrawal effects such as diarrhoea, irritability, occasional head twitches and paw tremors; in addition, for about 20 min after challenge, most of the animals attempted many times to leap out of the container in a co-ordinated manner.

Jumping was rarely seen in the following control animals: rats given subcutaneous injections of saline and challenged with saline or naloxone; rats chronically treated

TABLE 1. *Effect of naloxone in rats pretreated with morphine*

Pretreatment				Challenge		Responses within 15 min of challenge			
Drug	Dose range mg/kg	Days	No. of doses	Drug	Dose mg/kg	% of rats having diarrhoea	% of rats jumping	Mean no. of jumps/rat	No. of rats
M	10	1	1	N	0·25	8	8	0·31	13
M	10–14	2	4	N	0·25	80*	0	0	10
M	10–18	3	7	N	0·25	90*	20	1·70	10
M	10–25	4	10	N	0·25	93*	43*	0·86*	14
M	10–34	5	13	N	0·13	100*	60*	7·10*	10
M	10–34	5	13	N	0·25	85*	70*	6·47*	47
M	10–34	5	13	N	0·50	90*	60*	3·00*	10
M	10–34	5	13	N	1·00	100*	70*	4·90*	10
M	10–34	5	14	N	0·25	0	27	1·82	11
Last dose 30 min before challenge									
M	10–34	5	13	S	—	0	9	0·09	11
S	—	1	1	S	—	0	10	0·10	10
S	—	5	13	N	0·13–1·00	0	0	0	25

Morphine sulphate (M), naloxone HBr (N), or saline (S) given subcutaneously. Pretreatment given at 09.00, 12.00 and 16.00 h. Dose volume 10 ml. Challenge usually given 5 h after final pretreatment. Responses observed in plastic buckets. * Significantly different from control level ($P \leq 0.01$).