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Serum cholinesterase inhibition by omeprazole and lansoprazole

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Omeprazole inhibited human and rat serum cholinesterase by ~5 to 60% over the 0.5 to 50 mg/L (1.4–140 μM) concentration range. In contrast lansoprazole only produced 20–30% inhibition at the highest concentration of 10 mg/L (29 μM). Thus omeprazole but not lansoprazole is likely to potentiate the effect of succinylcholine at human clinical concentrations by inhibiting its hydrolysis *in vivo* by serum cholinesterases.

During general anaesthesia there is potential for aspiration of gastric contents. While the incidence is infrequent, it is nevertheless a major complication that is associated with high morbidity and mortality (Ruffalo et al. 1990). A gastric pH < 2.5 and a volume > 25 mL resulted in pulmonary damage in adult patients (Wilde et al. 1994). H_2 antagonists, antacids and drugs that modify gastric emptying have been used to reduce the pulmonary damage after aspiration of gastric contents (Machikanti et al. 1982). Proton pump inhibitors including omeprazole and lansoprazole are also recommended as anaesthetic premedication for this purpose (Gin et al. 1990; Hett et al. 1995).

Omeprazole interacts with neuromuscular blockers during anaesthesia; 0.5, 1 and 10 mg/kg iv doses in rats increased the steady-state neuromuscular paralysis induced with either atracurium or succinylcholine (Fu et al. 1994). Thus iv omeprazole at human therapeutic doses enhances the action of both a non-depolarising and a depolarising neuromuscular blocker both of which are dependent to varying extents on hydrolysis by serum cholinesterases for termination of their action.

The aim of this *in vitro* study was to elucidate the mechanism of this potentiation of succinylcholine's neuromuscular effect by examining if omeprazole inhibits serum cholinesterases that rapidly hydrolyse succinylcholine *in vivo*. Specifically the serum cholinesterase inhibitory effects of omeprazole and another proton pump inhibitor, lansoprazole, were examined using both rat and human serum as the serum cholinesterase enzyme source.

Omeprazole (5, 50 and 500 mg/L or 1.4, 14 and 140 μM) and lansoprazole (0.1, 1 and 10 mg/L or 0.29, 2.9 and 29 μM) at concentrations spanning the human therapeutic range (Clissold et al. 1986; Spencer et al. 1994) inhibited both human and rat serum cholinesterase activity in a concentration-dependent manner. Omeprazole inhibition was similar for the human and rat cholinesterase but lansoprazole inhibited the human enzyme substantially less than omeprazole. The known serum cholinesterase inhibitor, iso OMPA, at a concentration of 10.3 mg/L (29.5 μM), inhibited the human serum cholinesterase enzyme completely but the rat enzyme only partially (Table). The IC_{50} for omeprazole and lansoprazole (assuming linear relationships between cholinesterase inhibition and concentration), were substantially higher than that for iso-OMPA (Table).

Table: Serum cholinesterase inhibition by omeprazole and lansoprazole

Proton-pump inhibitor (mg/L, μM)	Inhibition (%) or IC_{50}	
	Human	Rat
Omeprazole		
0.5 (1.4)	5.5 ± 0.2	5.4 ± 0.1
5 (14)	14.0 ± 0.3	17.3 ± 0.2
50 (140)	58.8 ± 4.4	54.9 ± 1.7
IC_{50} mg/L	41.6 ± 1.3	44.4 ± 0.7
(μM)	116 ± 4	124 ± 2
Lansoprazole		
0.1 (0.29)	–	–
1.0 (2.9)	1.8 ± 0.03	7.1 ± 0.1
10 (29)	18.9 ± 0.7	29.9 ± 0.1
IC_{50} mg/L	26.4 ± 0.6	16.9 ± 0.3
(μM)	76 ± 2	49 ± 1
iso-OMPA		
10.3 mg/L (29.5 μM)	99 ± 8	24.6 ± 0.8
IC_{50} mg/L	2.8 ± 0.2	3.2 ± 0.3
(μM)	8.1 ± 0.5	9.4 ± 0.9

– No inhibition; Mean ± SEM for inhibition & IC_{50}

Experimental

Human and rat blood samples were collected from human volunteers and Sprague-Dawley rats and the harvested serum stored at −85 °C pending enzyme assays. Serum cholinesterase activity, in the absence or presence of various omeprazole or lansoprazole concentrations, was determined at 37 °C using a spectrophotometric method (Ellman et al. 1961). This involved hydrolysis of the substrate, acetylthiocholine, to yield thiocholine with subsequent reaction with 5,′5-dithiobis-2-nitrobenzoic acid yielding a yellow coloured anion (5-thio-2-nitrobenzoic acid), the formation rate of which was quantified over 10 min at 412 nm. The known serum cholinesterase inhibitor, tetraisopropyl pyrophosphoramide, iso-OMPA, was used as a positive control. The relative inhibition of enzyme activity, which was related to the rate of yellow colour generation, was calculated by comparing the slopes of the absorbance-time linear regression lines at different concentrations of the drug to the control (solvent only) slopes.

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