

A COMPARATIVE STUDY OF THE ACTIVITIES OF INDOMETHACIN GIVEN BY THE ORAL AND TOPICAL ROUTES IN THE RAT

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Non-steroidal anti-inflammatory drugs (NSAID), such as indomethacin, represent the first line of treatment for inflammatory joint diseases, but their use is frequently limited by side effects, in particular, the induction of gastric mucosal injury. Gastric damage is not due entirely to a local irritant action since ulceration occurs even with indomethacin administered rectally (Taylor et al, 1968).

In this study the potential of indomethacin, in a topically applied, hydro-alcohol gel was investigated in the rat. Oedema was induced by the sub-plantar injection of 0.1ml carrageenan (1%) 30 minutes after oral administration of 6mg/kg indomethacin or topical application to the paw of 300mg 1% indomethacin gel. Paw volume was measured using a mercury plethysmograph and % changes in volume compared to the starting volume are given in Table 1.

Table 1. The effect of indomethacin on carrageenan-induced paw oedema (% increase in paw volume \pm standard deviation, 5 animals per group)

Time after carrageenan injection (minutes)	120			180			240		
Control	30.9 \pm	9.18		43.6 \pm	9.26		57.9 \pm	8.93	
Indomethacin 6mg/kg Oral	19.0 \pm	7.14		26.9 \pm	6.42		28.2 \pm	6.16*	
Control	40.4 \pm	5.94		52.0 \pm	10.27		66.6 \pm	11.52	
Indomethacin 300 mg 1% gel/paw	32.4 \pm	10.56		39.2 \pm	10.18		40.4 \pm	7.89*	

* Significant difference from control $P < 0.005$

In a group of 5 animals given indomethacin 6mg/kg, orally a mean number of 13 gastric mucosal lesions per stomach was observed 2 hours after drug administration. At the same time topical application of 300mg 1% indomethacin gel failed to produce any observable damage to the gastric mucosa in any of the 5 rats examined.

Groups of 5 rats were pre-treated with indomethacin either orally (6mg/kg) or topically (300mg 1% gel to each hind paw) 30 minutes before carrageenan injection. The paw levels and serum levels were determined, 2 hours after the carrageenan administration, by the method of Skellern & Salole (1975), Table 2.

Table 2. Indomethacin levels 2.5 hours after drug administration (5 animals per group, drug administered 30 minutes before carrageenan)

	Serum $\mu\text{g ml}^{-1}$	Inflamed Paw	Normal Paw
		$\mu\text{g Paw}^{-1}$	$\mu\text{g Paw}^{-1}$
Indomethacin 6mg/kg by oral route	11.79 \pm 7.48	4.77 \pm 0.82	1.96 \pm 0.19
Indomethacin 300mg 1% gel/paw	2.97 \pm 1.39	5.71 \pm 2.28	3.29 \pm 1.14

Significant anti-inflammatory activity was detected for indomethacin given by either route of administration. Significantly lower serum drug levels were detected in rats given the drug by topical administration than by the oral route. The gastrototoxic effect of indomethacin was drastically reduced by giving the drug topically and there was no evidence of any local irritation to the skin. An anti-inflammatory drug preparation for topical application may offer significant advantages for clinical use in conditions where limited numbers of joints are affected.

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Taylor, R.T., et al (1968) Brit.Med.J. 4: 735

Skellern, G.C. & Salole, E.G. (1975) J.Chromatog. 114: 483