

## PHARMACOLOGY

## Antitussive Activity of Medazonamide

Most of the known antitussive agents also possess, in varying degree, other pharmacological properties, such as the analgesic, antihistaminic, local anaesthetic and spasmolytic ones (Silvestrini and Maffii<sup>1</sup>). These activities are often responsible for, or directly connected with, specific clinical side effects that may limit the effect. In particular, the antitussives that show analgesic effect produce depression of respiration and possibly tolerance, while antihistaminic antitussives often lead to drowsiness, and the local anaesthetic ones usually have a high toxicity.

For these reasons the search for new agents, possessing almost exclusively antitussive properties, is still pursued in many pharmacological laboratories. In the course of a systematic investigation on a new series of pyridazine compounds which have been prepared by Teotino and Cignarella<sup>2</sup>, it appeared that 2-methyl-4,5-dihydro-3-pyridazinone-6-carboxamide ('medazonamide') possesses antitussive properties in doses that do not produce any other pharmacological effect. Moreover, medazonamide was found to be practically non-toxic both in acute and chronic tests.

Medazonamide depresses and inhibits the cough induced in guinea-pigs by inhalation of acrolein vapours according to a method previously described<sup>1</sup>. Median effective doses and acute toxicity of medazonamide and some other known antitussive agents are given in Table 1.

Table 1. ANTITUSSIVE ACTIVITY (GUINEA-PIGS) AND ACUTE TOXICITY (MICE) OF MEDAZONAMIDE AND OTHER ANTITUSSIVE AGENTS

Compounds	Cough inhibition $ED_{50}$ (mg/kg s.c.)	$LD_{50}$ (mg/kg)	
		s.c.	i.v.
Codeine HCl	4	370 (ref. 3)	80 (ref. 3)
Morphine sulphate	5	311 (ref. 4)	255
Narcotine	3.5	390 (ref. 5)	—
Dextromethorphan	6	275 (ref. 3)	37 (ref. 3)
Benzononatine	3	230 (ref. 6)	9 (ref. 6)
Medazonamide	5	> 1,000	> 1,000

Medazonamide, at doses of 5 mg/kg subcutaneously, or 20 mg/kg orally, exerts inhibitory activity on coughing induced in dogs by aerosol of  $H_2SO_4$  (0.5 N), according to the method described by Winter and Flataker<sup>7</sup>.

Appreciable analgesic activity free from sedation is shown only at doses of 50 and 100 mg/kg subcutaneously and intraperitoneally in rats (method described by Randall and Selitto<sup>8</sup>) and mice (Eddy and Leimbach<sup>9</sup>). An intraperitoneal dose of 500 mg/kg of medazonamide produces significant inhibition of formalin-induced oedema of the rat hind-paw.

Frequency and amplitude of respiration are not modified after intravenous injection of 10 mg/kg of medazonamide in rabbits (anaesthetized with chloralose, 50 mg/kg intraperitoneally, and ethyl urethane, 1 g/kg subcutaneously) or after subcutaneous administration of 20 mg/kg in rats (anaesthetized with phenobarbitone, 120 mg/kg intraperitoneally). Arterial blood pressure of dogs (anaesthetized with pentobarbital sodium) is not changed by intravenous doses of 5 and 10 mg/kg.

At intravenous doses of 5 and 10 mg/kg medazonamide does not produce bronchial spasm in guinea-pigs. Codeine elicits bronchial spasm at doses of 7 mg/kg subcutaneously and 3.5 and 10 mg/kg intravenously.

At concentrations up to 10  $\mu$ g/ml. medazonamide is without any spasmolytic effect on contractions of isolated small intestine, induced either by barium chloride or acetylcholine (rat) or by histamine (guinea-pig).

Acute toxicity of medazonamide is extremely low (see Table 1). In fact, it causes no deaths in mice even after administration of 1 g/kg by various routes, and it differs, therefore, from all other known antitussive drugs, including the most recently discovered ones<sup>10,11</sup>.

In subacute and chronic toxicity tests, carried out in dogs at daily oral doses of 200 and 100 mg/kg for 4 weeks and 6 months respectively, medazonamide has been shown

to be well tolerated and free from side-effects even at high dose-levels and over prolonged treatment periods.

The results of the afore-mentioned pharmacological investigation demonstrate that medazonamide is an effective antitussive agent practically devoid of any pharmacological side-effects.

An extensive clinical study has shown that medazonamide significantly reduces the cough caused by chronic bronchitis in man (Nicolis and Pasquariello<sup>12</sup>). In 'double blind' conditions a dose of 800 mg of the substance appeared to be as effective as 60 mg codeine. The lack of any side-effect in man has been confirmed also for doses much higher than the effective ones.

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## Chloroquine in Dextran Oedema

EXPERIMENTS in our laboratory have shown that chloroquine blocks the actions of endogenous as well as exogenous histamine in guinea-pigs<sup>1</sup>. Chloroquine in these experiments was also found to block the action of exogenous 5-hydroxytryptamine (5HT). Further experiments were undertaken to study the action of chloroquine on the endogenous 5HT, which has been shown by several workers to be released by dextran in rats and mainly accounts for the oedema<sup>2,3</sup>. The cholesterol content of the adrenal glands of these rats was also estimated to determine whether the adrenals were involved in the action of chloroquine on dextran oedema.

A group of 10 male albino rats (100–150 g) were injected daily with chloroquine sulphate (10 mg/kg) intramuscularly. An equivalent amount of normal saline was injected into a similar group of 10 control rats. On the 31st and 38th day each animal was injected intraperitoneally with 1 ml. of 6 per cent dextran solution per 100 g body-weight. The dorsoplantar thickness was measured by means of a calliper rule as described by Setnikar *et al.*<sup>4</sup> to assess the degree of oedema. The animals were killed on the 45th day and the adrenal glands were removed. Total cholesterol was estimated by means of the Lieberman-Burchard reaction<sup>5</sup>. Results are summarized in Table 1.

It is seen from the table that chloroquine causes a reduction in the dextran oedema. That the oedema is not completely prevented shows a partial antagonism to the endogenous 5HT. These results are in conformity with *in vitro* results<sup>1</sup>. Chloroquine was found to cause a slight

Table 1. EFFECT OF CHLOROQUINE ON DEXTRAN OEDEMA AND ADRENAL CHOLESTEROL IN RATS

	Mean increase in dorso- plantar thickness (mm) $\pm$ (S.D.)	Mean cholesterol content of adrenals (g/100 g) $\pm$ (S.D.)
Control	2.33 $\pm$ 0.33 (2.0–3.0)*	2.66 $\pm$ 0.55 (1.87–3.62)
After chloroquine	0.87 $\pm$ 0.57 (0.0–1.5)	3.87 $\pm$ 1.08 (1.95–7.43)

\* Figures in the bracket indicate range.