63. Clinical trial of chlorpromazine (cpz) as a therapeutic antisecretory agent in cholera.

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Chlorpromazine (CPZ) has recently been shown to inhibit fluid secretion in experimental mice intestinal loops exposed to cholera toxin. It has also reduced intestinal fluid secretion in piglet diarrhoea induced by *E. coli* enterotoxin. The postulated mechanism of action is the agent's capacity to interfere with the stimulation of adenylate cyclase.

To test whether CPZ might be an effective anti-secretory agent in human cholera, a preliminary study was conducted in eight actively purging adult male cholera patients. Four patients received an oral dose and the other half an intramuscular dose. Within each group two patients received a low dose of 1 mg/kg body weight and two patients a high dose of 4 mg/kg body weight. Stool output was accurately measured before, during and after CPZ administration.

The mean rate of purging was 700 ml/hr during the 8 hours period immediately preceeding CPZ administration. During the first 8 hours immediately following the drug administration, the mean rate of purging was reduced to 350 ml/hr. The 8 hourly rates of purging further declined to 252 ml/hr and 127 ml/hr during the second and third 8 hour period respectively. This corresponds to a reduction of about 50 -70% of stool volume over the 24 hours following CPZ administration. When compared to a matched group of control cholera patients, the difference appeared to be highly significant without overlap between the test and the control group. No significant difference was observed in the response rate among the dose groups studied, except that patients who received CPZ 4 mg/kg intramuscularly showed an earlier and greater inhibitory effect than patients who received 1 mg/kg either orally or intramuscularly.

64. Inactivation of beef liver mitochondrial monoamine oxidase by acetylenic drugs and other reagents.

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The time-course of activity loss of the beef liver mitochondrial monoamine oxidase following reaction with acetylenic drugs, clorgyline, pargyline and deprenyl showed first-order kenetics with K_{app}-values of $1 \times 10^{-3}s^{-1}$, $1.8 \times 10^{-2}s^{-1}$ and $1.4 \times 10^{-2}s^{-1}$, respectively. This indicated that these drugs reacted with specific group(s) or component(s) of the enzyme, causing irreversible-inhibition (inactivation) due to the formation of enzyme-drug stable complexes.

Difference spectra of all the oxidase-acetylenic drug complexes (adducts) showed minima at 480 - 482 nm and 355 - 360 nm and a maximum at 412-416 nm and were similar to those reported for pargyline-inactivated bovine kidney enzyme and dimethylaminopropyne-inactivated bovine liver enzyme. These observations suggest that all the acetylenic drugs tested, reacted similarly with the isoalloxazine nucleus at the N-5 position of the FAD-cofactor of the enzyme irrespective whether they