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FURAZOLIDONE-PETHIDINE INTERACTION IN RABBITS

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1 The intravenous injection of pethidine in rabbits pretreated with furazolidone administered orally but not systemically resulted in severe interaction and fatal hyperpyrexia.

2 Treatment with *p*-chlorophenylalanine, chloropromazine or cyproheptadine protected the rabbits against the furazolidone-pethidine interaction, while α-methyl-*p*-tyrosine was ineffective.

3 5-Hydroxytryptophan produced a fatal hyperpyrexia in furazolidone pretreated rabbits.

4 Pretreatment of rabbits with 1,1,1-trichloro-2, 2-bis(*p*-chlorophenyl)ethane (DDT) accelerated and enhanced the furazolidone-pethidine interaction, while oxytetracycline pretreatment completely prevented the interaction.

5 It is concluded that furazolidone-pethidine interaction might depend mainly on potentiation of the effects of 5-hydroxytryptamine in the CNS and that the transformation of furazolidone into an active monoamine oxidase inhibitor metabolite might occur mainly in the gut microflora in the gut lumen.

Introduction

Furazolidone ((N-5-nitro-2-furfurylidene) 3-amino-2-oxazolidinone) is an antibacterial agent recommended for its local action in the intestinal tract and vagina (Ponce de Leon, 1957; Schneierson & Bryer, 1959). When administered to rats and man, furazolidone causes monoamine oxidase (MAO) inhibition (Stern, Hollifield, Wilk & Buzard, 1967; Pettinger, Soyangco & Oates, 1968), although it has no effect on this enzyme *in vitro*. A metabolite of furazolidone is thought to be responsible for the MAO inhibition (Stern *et al.*, 1967).

Since furazolidone is used extensively in tropical countries for the treatment of gastroenteritis, it was thought of interest to study its possible interactions with pethidine in rabbits. It is known that pethidine causes excitation and hyperpyrexia in rabbits pretreated with MAO inhibitors (Nymark & Nielsen, 1963; Loveless & Maxwell, 1965; Penn & Rogers, 1971; Fahim, Ismail & Osman, 1972; Sinclair, 1972). The symptoms in rabbits resemble those that occur in man, thus the rabbit seems to be a suitable model to use in this investigation. It was also the purpose of this work to investigate whether this interaction can be modified by pretreatment with drugs which interfere with the synthesis or antagonize the brain monoamines. In addition, experiments were carried out to see whether the interaction can be modified by pretreatment of rabbits with a broad spectrum antibiotic such as oxytetracycline or with an inducer of drug metabolizing enzymes such as 1,1,1-trichloro-2, 2,-bis(*p*-chlorophenyl)-ethane (DDT) to find out where biotransformation of furazolidone to the active MAO inhibitor takes place.

Methods

Rabbits of local strains and of either sex weighing between 1.5 and 2.5 kg were used. Furazolidone was administered orally by a stomach tube in a dose of 50 mg/kg daily for four successive days. Control rabbits received 10 ml of 0.9% w/v NaCl solution (saline) orally. On the fifth day, the animals were restrained in stocks and rectal temperatures were recorded at 15 min intervals with electrical thermocouples (Ellab electric universal thermometer, type T.E.3) inserted 5-7 cm into the rectum. When the temperature of a rabbit had been stable for 30 min, pethidine (5 mg/kg) was slowly injected via a marginal ear vein. The experiments were carried out at 21-22° C.

The effect of pethidine was also tested in furazolidone-treated animals which had also received one of the following pretreatments:

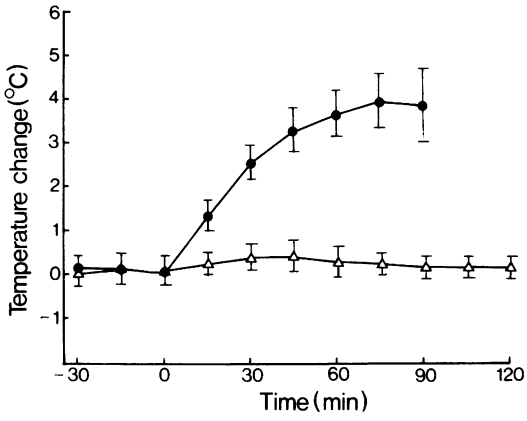

Figure 1 Effect of pethidine on the rectal temperature of rabbits pretreated with furazolidone. Pethidine (5 mg/kg i.v.) was injected at time zero in one group of five rabbits (•), the other group of four rabbits was pretreated with furazolidone and injected with saline (△). Doses are given in the text. Vertical lines indicate s.e. mean.

chloropromazine hydrochloride or cyproheptadine hydrochloride (5 mg/kg, i.v.) 30 min before pethidine; *p*-chlorophenylalanine (PCPA) (125 mg/kg i.p.) 66, 42, and 18 h before pethidine; α-methyl-*p*-tyrosine (80 mg/kg i.p.) 48, 36, 24 and 12 h before pethidine; oxytetracycline (50 mg/kg i.p.) twice daily and also once daily orally (50 mg/kg) for seven days before pethidine; DDT (50 mg/kg i.p.) injected daily for four successive days before furazolidone pretreatment. 5-Hydroxytryptophan (5-HTP) (60 mg/kg) was injected intravenously.

Drugs

The following drugs were used: *p*-chlorophenylalanine (Sigma), chloropromazine (May & Baker), cyproheptadine (Merck, Sharp & Dohme), furazolidone (Eaton), 5-hydroxytryptophan (Sigma), α-methyl-*p*-tyrosine (Sigma), oxytetracycline (Pfizer), pethidine (Evans), and 1,1,1-trichloro-2, 2-bis(*p*-chlorophenyl)ethane (DDT) (B.D.H.). The doses given in the text refer to the salts, whenever applicable.

Results

Rabbits treated with furazolidone, pethidine, *p*-chlorophenylalanine, α-methyl-*p*-tyrosine, cyproheptadine, 5-HTP, oxytetracycline, or DDT did not show any significant change in their body temperature when compared with saline-treated control animals.

Furazolidone-pethidine interaction

Pethidine injection produced motor restlessness, shivering like tremor, hyperexcitability, tachypnoea and hyperpyrexia in furazolidone pretreated rabbits (Figure 1). The mean increase in temperature was 3.9°C, 75 min after pethidine injection and 3 out of 5 rabbits died in hyperpyrexia. Control rabbits receiving saline orally when injected with pethidine did not show any significant rise in their temperature. Also rabbits pretreated with furazolidone and injected with saline did not show any significant change in their temperature. In some rabbits furazolidone was injected subcutaneously in a dose of 50 mg/kg daily for four successive days and this resulted in a very mild interaction when pethidine was injected on the fifth day.

Pretreatment with p-chlorophenylalanine, cyproheptadine, chloropromazine, and α-methyl-p-tyrosine. Interaction of furazolidone with 5-hydroxytryptophan

The furazolidone-pethidine hyperpyrexic interaction was completely prevented by PCPA treatment and none of the rabbits pretreated with PCPA died in hyperpyrexia. Similarly the injection of either cyproheptadine or chloropromazine in furazolidone pretreated rabbits 30 min before pethidine injection protected the rabbits against the fatal hyperthermia. The injection of chloropromazine alone in rabbits resulted in some significant fall in their body temperature ($P < 0.05$).

The injection of the 5-hydroxytryptamine (5-HT) precusor, 5-HTP in furazolidone pretreated rabbits, resulted in motor restlessness, excitation, tremors and hyperpyrexia which caused the death of 3 out of 4 animals (Figure 2).

There was no protection against the furazolidone-pethidine interaction following pretreatment of the rabbits with α-methyl-*p*-tyrosine (Figure 2) and 2 out of 4 rabbits died in hyperpyrexia 75 min after pethidine injection.

Pretreatment with oxytetracycline or DDT

Pretreatment of rabbits with oxytetracycline resulted in complete protection against the furazolidone-pethidine interaction (Figure 3). On the other hand, pretreatment of rabbits with DDT resulted in acceleration and potentiation of the interaction. Thus there was fatal hyperpyrexia after three days of furazolidone treatment instead of the usual four days period, and 5 out of 6 animals died in hyperpyrexia. Even after two days of furazolidone administration motor restlessness,

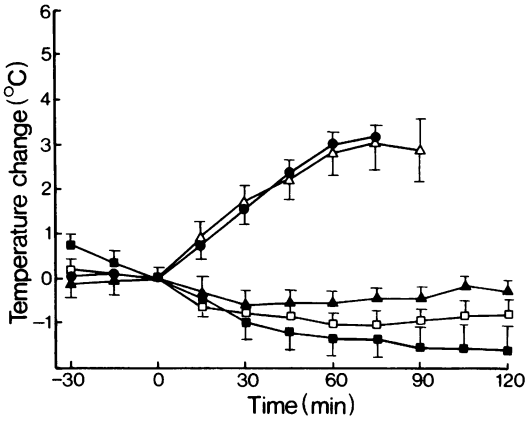

Figure 2 Effects of pretreatment of rabbits with *p*-chlorophenylalanine (PCPA), cyproheptadine, chloropromazine or α-methyl-*p*-tyrosine on the furazolidone-pethidine interaction and interaction of furazolidone with 5-hydroxytryptophan (5-HTP). Pethidine (5 mg/kg i.v.) was injected at time zero in all experimental groups except one (●), where 5-HTP was injected instead. All rabbits were pretreated with furazolidone; in addition the following drugs were administered at the times and doses indicated in the text: PCPA (▲), cyproheptadine (□), chloropromazine (■), α-methyl-*p*-tyrosine (△). Each curve represents the mean response from four rabbits. Vertical lines indicate s.e. mean.

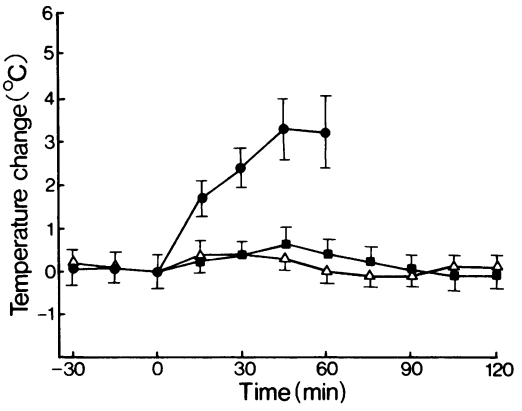

Figure 3 Effects of oxytetracycline or DDT on the furazolidone-pethidine interaction. Pethidine (5 mg/kg i.v.) was injected at time zero in all experiments. (●) Rabbits pretreated with both DDT and furazolidone (six rabbits); (△) rabbits pretreated with both oxytetracycline and furazolidone (five rabbits); (■) rabbits pretreated with DDT alone (four rabbits). Vertical lines indicate s.e. mean.

severe tremor and hyperexcitability were precipitated in DDT pretreated rabbits by pethidine injection but there was no significant hyperpyrexia. DDT pretreatment alone followed by pethidine injection resulted in the immediate precipitation of tremor-like convulsions, loss of righting reflex and some non-significant hyperpyrexia (Figure 3). The rabbits recovered completely 60 min later.

Discussion

Furazolidone is used as a local antibacterial agent for the treatment of gastroenteritis in tropical regions. Its MAO inhibiting properties have been described in rats and man by Stern *et al.* (1967) and Pettinger *et al.* (1968). The use of furazolidone for more than five days in patients is not advised since it may subject them to the hazards of hypertensive crises (Pettinger *et al.*, 1968). Although it is not itself a MAO inhibitor, it is believed to be converted to an active metabolite, possibly 2-hydroxyethyl hydrazine, in the rat (Stern *et al.*, 1967). However, Pettinger *et al.* (1968) failed to detect any metabolite which possessed MAO inhibiting properties in the urine from patients treated with furazolidone.

In the present studies it was possible to demonstrate signs of hyperexcitability, motor restlessness and slight hyperpyrexia in rabbits when pethidine was injected after only two days of furazolidone pretreatment. However, severe interaction and fatal hyperpyrexia resulted when pethidine was injected into rabbits pretreated for four days with furazolidone administered orally. The following results suggest that 5-HT is involved in the interaction occurring between furazolidone and pethidine. Pretreatment with PCPA, which selectively depletes brain 5-HT (Koe & Weissmann, 1966), completely prevented the fatal hyperpyrexic interaction. Also both chloropromazine and cyproheptadine antagonized the furazolidone-pethidine interaction and protected the rabbits. On the other hand the injection of 5-HTP in doses which had little effect on temperature in normal rabbits (Sinclair, 1973) produced severe and fatal hyperpyrexia in furazolidone pretreated rabbits. Fahim *et al.* (1972) have shown that pretreatment with drugs like lithium and yohimbine which increase 5-HT concentration in the brain caused pethidine to provoke a hyperpyrexic response in rabbits. Depletion of brain catecholamines by pretreatment with α-methyl-*p*-tyrosine had no effect on the furazolidone-pethidine interaction.

Pethidine, the tricyclic antidepressants, some antihistamines and dextromethorphan have been shown to block the neuronal uptake of 5-HT

(Carlsson, Corrodi, Fuxe & Hokfelt, 1969; Carlsson, Jonason & Lindqvist, 1969; Carlsson & Lindqvist, 1969; Sinclair, 1973). All of these agents exhibit a characteristic interaction with MAO inhibitors in rabbits (Nymark & Nielsen, 1963; Loveless & Maxwell, 1965; Penn & Rogers, 1971; Fahim *et al.*, 1972; Sinclair, 1972, 1973).

The exact site where conversion of furazolidone into the active metabolite takes place is not known with certainty (Stern *et al.*, 1967). Both the intestinal mucosa and the liver have been suggested as primary sites for biotransformation of furazolidone. Pretreatment of the rabbits with oxytetracycline, which inhibits the gut microflora completely, antagonized the furazolidone-pethidine interaction and prevented the fatal hyperpyrexia. In addition, when furazolidone was injected subcutaneously in a dose of 50 mg/kg daily for four successive days into rabbits, this resulted only in a mild interaction with no hyperpyrexia when pethidine was injected. These findings suggest that the intestinal microflora, rather than the gut wall, is the main site for transformation of furazolidone into the active MAO inhibitor metabolite. Walker (1970) has shown that the liver is not the only site for azo compounds reduction, for the gut microflora also plays an important role in this reaction. It has been shown by Gingel, Bridges & Williams (1971) that pretreatment of rats with antibiotics results in a marked decrease of azo reduction of neoprontozil or prontozil to sulphanilamide.

On the other hand pretreatment with the known drug-metabolizing enzyme inducer, DDT (Hart & Fouts, 1963), resulted in the enhancement, potentiation and acceleration of the furazolidone-pethidine interaction. It is unlikely that DDT enhances transformation of furazolidone by the gut microflora. However, although furazolidone is poorly absorbed from the gut, enough may reach the liver to be more efficiently transformed following treatment with DDT.

The use of furazolidone on long-term basis in diseases such as chronic ulcerative colitis, gastroenteritis and in typhoid carriers has been considered in tropical countries. In the light of the above evidence the use of furazolidone for even a few days may carry the risk of serious interaction with many agents, especially in patients exposed to the pesticide DDT and other persistent halogenated pesticides that induce drug-metabolizing enzymes.

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