SOME ANTIPYRETICS RELATED TO ASPIRIN AND PHENACETIN

BY J. A. BAKER, J. HAYDEN, P. G. MARSHALL, C. H. R. PALMER* AND T. D. WHITTET

From the Nicholas Research Institute, Ltd., and the Pharmaceutical Department, University College Hospital and Medical School, London

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ASPIRIN and phenacetin are good analgesics and antipyretics, about whose defects, however, there is now considerable evidence. In small doses, both cause sensitisations, which may be trivial like skin rashes or fever, or severe like the blood dyscrasias or kidney damage. Also aspirin in large doses causes gastric bleeding. We have synthesised a number of substances related to aspirin and to phenacetin and have examined their pharmacology. In this communication we describe shortly their preparation, their acute toxicity and their antipyretic activity.

Benz-1,3-oxazine-2,4-dione. Carsalam was prepared by the method of Einhorn and Mettler (1902) with minor modifications. The product had m.p. 228° (lit., 227°).

m-*Ethoxyacetanilide.* The method of Reverdin and Lokietek (1915) was used substituting diethyl sulphate for ethyl bromide. The product had m.p. 97–98°.

m-*Hydroxyacetanilide* was prepared by the action of acetic anhydride on *m*-aminophenol (Reverdin and de Luc, 1914); m.p. 148–149°.

m-*Allyloxyacetanilide.* This was prepared essentially by the method of Arnold, McCool and Schultz (1942); m.p. 86–87° (lit., 87–88°).

m-*n-Pentyloxyacetanilide.* This was prepared in a similar fashion to the above by the action of n-pentyl bromide on *N*-acetyl-*m*-aminophenol. The material crystallised in colourless needles from light petroleum (b.p. 60–80°); m.p. 77°. Found: C, 70·1; H, 8·8; N, 6·0 per cent. $C_{12}H_{19}O_2N$ requires C, 70·6; H, 8·7; N, 6·3 per cent.

Acute Toxicity

Carsalam in mice. Groups of 5 fasted mice were given a single oral dose of 0·67 to 3·3 g./kg. suspended in 5 per cent acacia mucilage and the number of deaths within 5 days was recorded.

Carsalam in rats. Groups of 10 male rats were treated orally with 0·35 to 1·0 g./kg. in 5 per cent acacia mucilage (2 ml./100 g.) and the number of deaths within 5 days was recorded. All results were calculated by the method of Karber (1931) and Miller and Tainter (1944).

m-*Ethoxyacetanilide* was administered orally in a 5 per cent acacia mucilage to groups of not less than 10 mice.

* Present address: School of Pharmacy, Leicester College of Technology.

Antipyretic Action

Carsalam, aspirin, chlorthenoxazine and salicylamide were compared by a modification of the method of Brownlee (1937). The drugs were given orally and the pyrogens injected immediately afterwards instead of giving the antipyretics 2 hr. after the pyrogens.

Groups of 3 rabbits were given by stomach tube, 500 mg./kg. of one or other of the drugs in suspension in 5 ml./kg. of 2 per cent acacia mucilage containing 0·1 per cent of polysorbate 80. Other groups were given the mucilage as controls. Immediately afterwards each animal was injected into an ear vein with 1·0 ml./kg. of TAB vaccine (protein shock, 500 million organisms per ml.). The rabbits had been deprived of food but not water overnight and both were withheld during tests. Temperatures were recorded with a thermistor apparatus (Whittet, 1958) every 15 min. for at least 1 hr. before and 3 hr. after treatment. The tests were repeated as cross-overs until each of 12 rabbits had received each drug and the control. The temperatures are plotted as a comparison with the controls as a straight line at 0° (Brownlee, 1937) in Fig. 1. From the curves the reduction in temperature can be calculated graphically in a manner similar to that used for fever indices (Beeson, 1947). We have called these "antipyretic indices"; they are shown in Table I.

TABLE I

ANTIPYRETIC INDICES (3 HR.) OF CARSALAM, PHENACETIN AND RELATED DRUGS

Drug	Antipyretic index
Carsalam	270 (12)
Aspirin	143 (12)
Salicylamide	35 (12)
Chlorthenoxazine	−1 (12)
Phenacetin	70 (12)
Paracetamol	150 (12)
m-Ethoxyacetanilide	152 (36)
m-Hydroxyacetanilide	120 (12)
m-Allyloxyacetanilide	108 (24)
m-n-Pentyloxyacetanilide	64 (24)

Figures in parenthesis are number of tests.
The antipyretic index is the amount of reduction of fever, compared with controls, caused by a drug in a definite period after treatment with the antipyretic and injection with pyrogens (3 hr. in the above cases.) It is measured by plotting the control as a straight line at 0° and the temperatures of animals given antipyretics as differences from this. The area between the control and temperature-reduction line gives a measure of the antipyretic effect.

Further groups of 3 rabbits were given, by the same technique, doses of 50, 100, 200 and 400 mg./kg. of carsalam, of aspirin and of 5 ml./kg. of mucilage as controls. Each was injected with 0·1ml./kg. of TAB vaccine. The antipyretic indices were again determined graphically (Table II).

Carsalam had an appreciable hypothermic effect and this action was therefore compared with that of aspirin. Groups of 3 rabbits were given 50, 100, 200 and 400 mg./kg. of carsalam and 50 and 400 mg./kg. of aspirin and their temperatures were recorded for at least 1 hr. before and 4½ hr. after treatment. The tests were repeated as cross-overs. The mean temperature changes were plotted against time for 4½ hr. after treatment and the amount of hypothermia produced by each dose during that period was measured graphically. We have called this the "hypothermic index". (Table II).

TABLE II

ANTIPYRETIC AND HYPOTHERMIC INDICES FOR VARIOUS DOSES OF CARSALAM AND ASPIRIN

Dose mg./kg.	Antipyretic index*		Hypothermic index†	
	Carsalam	Aspirin	Carsalam	Aspirin
50	− 48 (12)	23 (12)	37 (12)	− 23 (6)
100	− 10 (12)	− 18 (12)	62 (12)	—
200	37 (12)	82 (12)	161 (12)	—
400	172 (12)	145 (12)	201 (12)	13 (6)

Figures in parenthesis are number of tests.
* Three hr.
† The hypothermic index is the amount of reduction in temperature as compared with the initial temperature, in a definite period after treatment with the drug (4½ hr. in the above instances). It is determined by measuring the area between the mean initial temperature drawn as a straight line and the curves showing changes in temperature.

Tests were also carried out by the original Brownlee method using doses of 500 mg./kg. of carsalam and 0·1 ml./kg. of vaccine.

m-*Hydroxyacetanilide derivatives.* The antipyretic activities of these compounds were compared with those of phenacetin and paracetamol by the modified Brownlee method. The temperature changes are plotted as a comparison with the controls as a straight line at 0° in Fig. 2. Their antipyretic indices are shown in Table I. Tests were also made on *m*-ethoxyacetanilide by the original Brownlee method using 500 mg./kg. of the compound and 0·1 ml./kg. of TAB vaccine.

RESULTS AND DISCUSSION

Carsalam

Acute toxicity. The oral toxicity to mice was between 1·0 and 1·5 g./kg. This is similar to that of aspirin (Spector, 1956, gives 1·1 g./kg.) but that found for rats, 750 mg., was much greater than that of aspirin (Spector gives 1·36 g./kg.). This significant species difference is not unusual but the compound needs to be tested further on different species.

Antipyretic action. Carsalam has approximately 1·7 times the antipyretic effect of aspirin in a dose of 500 mg./kg. (Fig. 1). Salicylamide and chlorthenoxazine had little antipyretic action in this dose.

Hypothermic action. Carsalam 50 mg./kg., produced a reduction of temperature of approximately 0·6° for about 1½ hr. after oral administration and with a dose of 400 mg./kg. the temperature was nearly 2° below its initial value after 4½ hr. The original Brownlee method showed that carsalam in doses of 500 mg./kg. rapidly reduced fever already present. Rabbits given doses of 400 to 500 mg./kg. of carsalam showed marked diuresis and frequently became limp for a few hours.

m-*Hydroxyacetanilide Derivatives*

Acute toxicity of m-*ethoxyacetanilide.* Doses of 200 and 500 mg./kg. of this compound caused no deaths and a further dose of 1 g./kg. caused only 1 death in a group of 20 mice. The oral LD50 for mice is, therefore, clearly considerably greater than 1 g./kg.

The antipyretic indices obtained from Fig. 2 show that *m*-ethoxyacetanilide has an effect about twice that of phenacetin and similar to

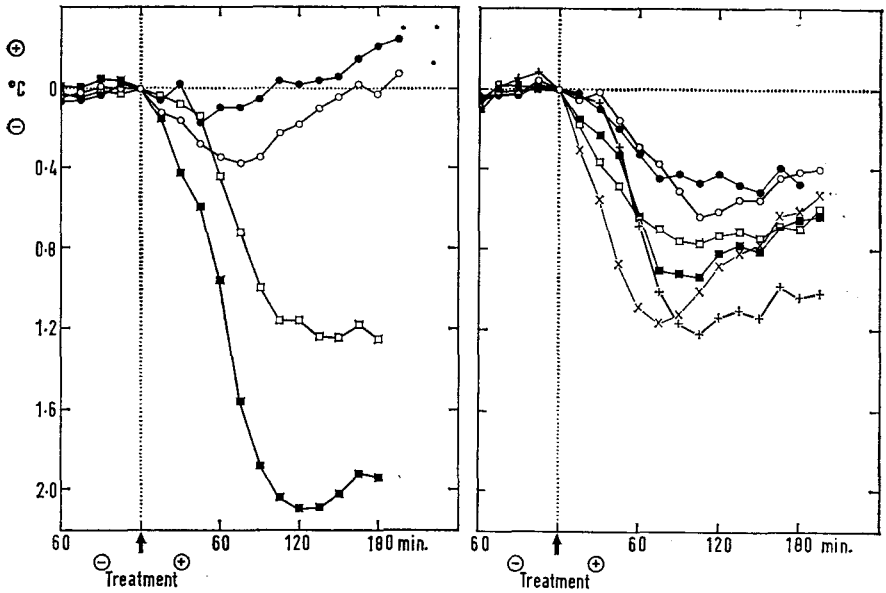

FIG. 1. Antipyretic action of carsalam, aspirin, chlorthenoxazine and salicylamide Control at 0° C. ■—■ = Carsalam. □—□ = Aspirin. ●—● = Chlorthenoxazine. ○—○ = Salicylamide. Each point is the mean of 12 tests.

FIG. 2. Antipyretic action of phenacetin, paracetamol and compounds 747, 749, 875 and 880. Controls at 0° C. 48 tests. ○—○ = Phenacetin 12 tests. +—+ = Paracetamol 12 tests. ×—× = *m*-ethoxyacetanilide 36 tests. ■—■ = *m*-hydroxyacetanilide 12 tests. □—□ = *m*-allyloxyacetanilide 24 tests. ●—● = *m*-pentyloxyacetanilide. 24 tests.

that of paracetamol. The effect of the allyloxy derivative is approximately 50 per cent greater than that of phenacetin, whilst the n-pentyloxy compound is slightly less effective. By the original Brownlee method *m*-ethoxyacetanilide 500 mg./kg., rapidly reduced fever already present.

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The paper was presented by DR. WHITTET.