

ANTIPYRETIC ACTIVITY OF FLURBIPROFEN

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SYNOPSIS

A randomised double-blind study to compare the antipyretic activity between flurbiprofen, a nonsteroidal drug, and aspirin was carried out in hospital patients with fever from various causes. Thirteen patients received a single dose of flurbiprofen, 25 mg, and 12 patients received a single dose of aspirin, 300 mg. The mean temperature of both groups of patients were recorded hourly for 8 hours and then at the 12th hour after administration.

Flurbiprofen was found to produce a greater fall in mean temperature than aspirin throughout the period of the trial but it was at the 8th hour that differences in fall of temperature reaches a significant level. The antipyretic effect of flurbiprofen was maximum at the 4th hour with a record drop of 1.46° C and the effect was sustained for the next 6 hours. Aspirin also produced a fall in temperature but the degree of fall was not marked and the duration of fall was shorter.

It would appear that flurbiprofen is a better antipyretic drugs since clinical trials elsewhere have shown that it has very few side-effects when compared to aspirin.

INTRODUCTION

Flurbiprofen or 2-(2-fluoro-4-biphenyly) propionic acid is a new member of the phenylalkanoic series. Like its predecessors, it has been shown to possess significant analgesic, anti-inflammatory and antipyretic properties in the laboratory and in the clinics (Adams & McCullough, 1971; Glenn et al, 1973; Masumoto & Takase, 1973; Thompson et al, 1973; Chalmers et al, 1972).

Although the analgesic and anti-inflammatory activities of flurbiprofen have been extensively studied in patients with rheumatoid arthritis, osteoarthritis, soft-tissue rheumatism and others (Rossel, 1973; Cardoe, 1973; Lane, 1973), the antipyretic property of this drug has only been investigated in animals. Adam et al (1975) using yeast-fevered rats found

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that the lowest effective dose to inhibit pyrexial action was 0.12 mg/Kg for flurbiprofen and 25 mg/Kg for aspirin—a 200 times potency weight for weight.

In man, the antipyretic action of flurbiprofen has not been investigated and thus the present study was designed to evaluate the antipyrexial potency of this drug in a comparison with aspirin, a standard antipyretic agent.

MATERIAL AND METHODS

This was a randomised double-blind study involving 25 adults of both sexes and ages ranged from 11 to 60 years. All presented with a fever of over 38° C and were allocated to treatment schedules at random. Temperature was recorded in each patient by a clinical thermometer kept sublingually for one minute. The same thermometer was used for all patients. Temperature reading was recorded in Celcius (° C). Two readings were taken each time, the second being 5 minutes after the first and the mean temperature was calculated.

After recording the initial mean temperature, each patient was given a single dose of identical-looking capsule of either 25 mg of flurbiprofen or 300 mg of aspirin. No second dose of the drug was given and other drugs were not allowed until after the trial. After oral administration of the drug, the temperature of each patient was recorded at ½, 1, 2, 3, 4, 5, 6, 8 and 12 hours. Any adverse reactions found were noted.

RESULTS

Of the 25 patients, 13 received flurbiprofen and 12, aspirin. The causes of the pyrexia were viral fever (5 patients), urinary tract infection (4), chest infection (3), drug fever and rheumatic fever (2 each), hepatitis, typhoid fever, acute glomerulonephritis, bacterial endocarditis, viral encephalitis, malaria, pyoderma, rheumatoid arthritis and systemic lupus erythematosus (one each).

The mean temperature and the mean fall in temperature of both the flurbiprofen and the aspirin groups are shown in the Table and also graphically represented in Figs. 1 and 2 respectively.

(a) Mean Temperature

The initial mean temperature for flurbiprofen and aspirin was 38.46° C and 38.69° C respectively, there being no statistical significant difference between the two readings. In both groups, rapid

FIGURE 1

MEAN TEMPERATURE

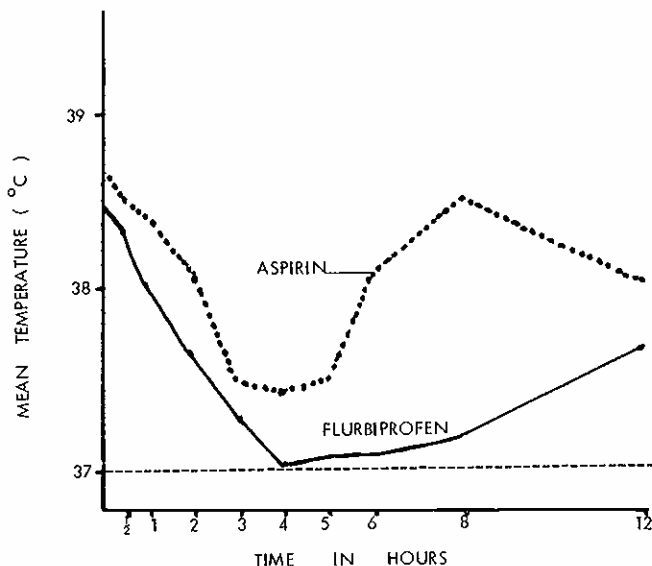
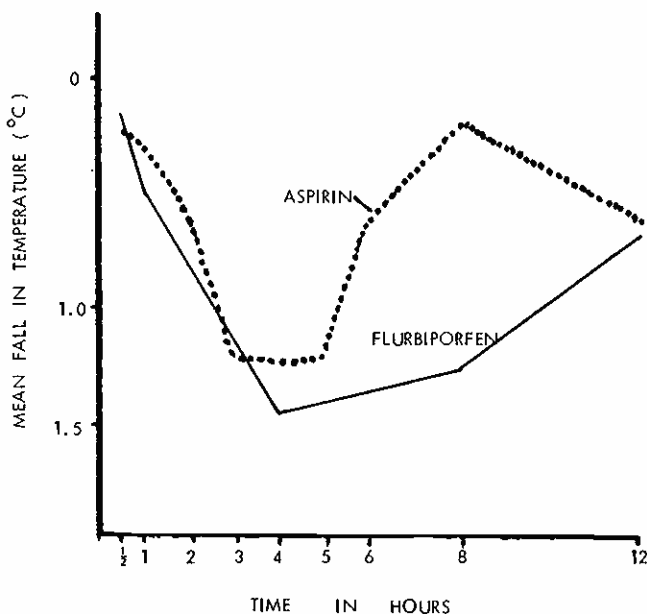


FIGURE 2 MEAN FALL IN TEMPERATURE



fall in the temperature was noted soon after oral administration and it was observed that the fall was more marked with the flurbiprofen than with aspirin throughout the whole trial. With flurbiprofen, the mean temperature dropped to normal (37.0° C—37.18° C) at 4 hours and remained at that level until after 8 hours, when the mean temperature slowly rose to 37.69° C at the 12 hours. With aspirin, the drop in mean temperature was more rapid, reaching 37.49° C at 3 hours and 37.46° C (the maximum fall) at the 4th hour. It remained at the same level until after the 5th hour when the

TABLE I—Mean Temperature and Mean Fall in Temperature

Time (Hours)	Flurbiprofen (n = 13)		Aspirin (n = 12)	
	Mean Temp. (° C)	Mean Fall in Temp. (° C)	Mean Temp. (° C)	Mean Fall in Temp. (° C)
0 (Initial)	38.46	—	38.69	—
½	38.33	0.13	38.49	0.20
1.	38.01	0.45	38.41	0.28
2.	37.62	0.84	38.12	0.57
3.	37.28	1.19	37.49	1.20
4.	37.00	1.46	37.46	1.23
5.	37.05	1.41	37.48	1.21
6.	37.09	1.37	38.07	0.62
8. #	37.18	1.28#	38.50	0.19#
12.	37.69	0.77	38.07	0.62

p < 0.05

temperature rebounded and almost returned to its initial temperature at 8 hours—38.50° C. After this, the temperature again dropped for the second time, recording 38.07° C at the 12 hours.

(b) Mean Fall in Temperature

As shown in Figs. 1 and 2, the mean fall in temperature of both groups corresponds closely to that of the mean temperature at different point of time. The maximum fall in temperature for flurbiprofen was 1.46° C at the 4th hour. For aspirin, it was 1.23° C also at the same time. The fall in temperature after the 4th hour remained low and sustained for the next 4 hours in the flurbiprofen group. For the aspirin group, the mean fall in temperature was reduced from 1.23° C at the 4th hour to 0.19° C at the 8th hour and 0.62° C at the 12th hour.

(c) Rate of Fall in Mean Temperature

(Value of the slope)

The rate of fall in temperature in both groups during the first 5 hours was 0.736 for flurbiprofen and 0.335 for aspirin (p > 0.05; N.S.).

(d) Degree of Fall in Mean Temperature

In both groups, the degrees of fall in mean temperature from the initial temperature to the last recording at 12 hours were found to be similar without any statistical difference in the ½, 1, 2, 3, 4, 5, 6, 7 and 12 hours. However, at the 8th hour, a significant difference (p < 0.05) was found

between the two groups. The mean fall in temperature for flurbiprofen then was 1.28° C and that for aspirin was 0.19° C.

The average maximum fall in temperature for the first drug was 1.72 ± 0.67° C, while that for aspirin was 1.57 ± 0.84° C (p > 0.05; N.S.).

(e) Duration of Fall in Temperature

The average duration of fall in temperature for flurbiprofen was 6.08 ± 2.4 hours. For aspirin, it was 5.42 ± 2.45 hours (p > 0.05; N.S.).

(f) Side-effects

These were found in both groups of patients.

DISCUSSION

Like its predecessors ibufenac and ibuprofen, flurbiprofen has been shown to possess potent analgesic, anti-inflammatory and antipyretic properties in animals and in man. Adams & McCullough (1971) revealed that flurbiprofen is at least 10 times more potent than ibuprofen and other non-steroidal anti-inflammatory drugs. This drug is rapidly absorbed in the gut with peak levels occurring 60 to 90 minutes after administration. In the blood, it is protein-bound but does not accumulate in the circulation to any significant extent after prolonged dosing. The inhibitory effect of this drug is not dependent on glucocorticoid activity but possibly on its action on the hepatic microsomal enzymes (Chalmer et al, 1973).

In most pharmacological systems, it is often not possible to compare directly the exact potency of a new drug against a standard compound such as aspirin, because there are marked differences between the dose-response curves. In animal experiments, Adams et al (1975) used the lowest effective dose of a drug that can achieve a significant pharmacological effects such as analgesic, anti-inflammatory or antipyretic activity, to compare with the same dose of another drug in pharmacologic potency.

Thus they have found that the lowest effective dose for flurbiprofen was 0.25 mg/Kg and for aspirin was 80 mg/Kg—for achieving the same anti-inflammatory result on the ultraviolet-induced erythema of the guinea pig skin. For analgesic control, using the inflamed paws of rat, the lowest effective dose for flurbiprofen was 0.33 mg/Kg and that for aspirin was 90 mg/Kg. For antipyretic effect, using the yeast-fevered rats, the lowest effective dose of flurbiprofen was 0.12 mg/Kg and that for aspirin was 25 mg/Kg. Tran-

slating these results to man, flurbiprofen was found to be 60 to 700 times more potent than aspirin in all these pharmacological effects (Masumoto & Takase, 1973).

However, in clinical trials, the pharmacological effects were different from those found in the animals test systems. Smaller dosage of flurbiprofen—between 15 to 60 mg, were found to be ineffective in treating patients with rheumatoid arthritis (Morinaga et al, 1973). If the dosage was increased to 100 or 200 mg a day, the result achieved in the treatment of rheumatoid arthritis was same to those who were treated with 3 to 3.6 gm of aspirin a day (Laine, 1973; Owen, 1973). Thus the potency of the former drug is about 20 to 30 times that of the latter.

Since the antipyretic activity of flurbiprofen has not been evaluated in human with fever from various causes, the present study was undertaken to determine the antipyretic effectiveness of 25 mg of flurbiprofen in comparison to 300 mg of aspirin. Both drugs are the smallest single dose tablet of their kind. Our result confirms that 25 mg of flurbiprofen has a more potent antipyretic action than 300 mg of aspirin. Flurbiprofen produced a more significant drop in the mean temperature than the aspirin group throughout the 12 hours of recording. Although both groups showed a maximum fall in mean temperature at the 4th hour, the temperature recorded from flurbiprofen was much lower (37.0° C).

Although the rate, degree and duration of fall in temperature between two groups were similar in almost the whole of the trial period, there were some important observations in this study that merit discussion. The temperature fall in flurbiprofen seemed to be sustained and remained low (around 37.0 and 37.18° C) from 4th to the 8th hour while the temperature fall for aspirin lasted only 2 hours and showed a rebound to its original reading during the 8th hour. Thus at 8th hour, there was a statistical difference between the degree of temperature fall of the two drugs.

The difference in the dose-responses curves of the two drugs in this study may be related to the

drug absorption, circulation and inactivation in the human body. A larger dose of aspirin might produce a different temperature pattern, but side-effects will be increased.

However, it is important to know that now we have a new antipyretic drug with more potent action than aspirin and with very few side-effects even though it was used in very high dosage elsewhere for the treatment of rheumatoid arthritis and other arthritis (Chalmers et al, 1972; Glick, 1973).

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