USES AND ABUSES OF ANTIPYRETIC THERAPY

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Fever is undoubtedly the most common symptom confronting the physician who treats children. It is fought as though it were the patient's primary disease, and its mere presence is often accepted as being sufficient indication for the institution of antipyretic therapy. It is not surprising, therefore, that therapeutists and pharmaceutical concerns have energetically sought new and better drugs for the control of fever. In the past few years there has appeared on the market a number of new formulations which are purported to offer distinct advantages in terms of antipyretic potency, acceptance by children, and/or reduced toxicity.

It is axiomatic that virtually any claim regarding a drug can be supported by published data, if the proper study is selected and interpretation is sufficiently influenced by conviction. Particularly is this true of antipyretic-analgesic drugs, where such factors as lability in the case of fever and lack of objectivity in the case of pain, make evaluation difficult. The claims and counterclaims which have been made concerning antipyretic drugs have led to considerable confusion and misunderstanding on the part of clinicians in general. The purpose of this presentation is to attempt to provide some clarification of this problem.

IS ANTIPYRESIS INDICATED?

More critical than the choice of an antipyretic is the question of whether or not such therapy is indicated in the individual case, for there is little doubt that these drugs are grossly overused, at times to the detriment of the patient. Therefore, before discussing the antipyretics themselves, it seems appropriate to review briefly a number of points which deserve consideration before one elects to use an antipyretic.

DuBois summarized a lifetime of study on fever and the regulation of body temperature with the statement: "Fever is only a symptom and we are not sure that it is an enemy. Perhaps it is a friend." The literature concerning the possible role of fever in body defenses is extensive and inconclusive. There is little question that artificially induced fever is of some value in the treatment of such diseases as neurosyphilis, certain inflammations of the eye, and arthritis. In animal experiments, elevation of body temperature has been shown to be of importance in resistance to certain infections.

Body temperatures of greater than 106°F (41.1°C) rarely occur except under highly anomalous circumstances, and this level is probably safely below the point at which temperature itself poses an immediate threat to the individual. Circumstances which may lead to higher temperatures include: exposure to a sudden overwhelming heat load, such as injection of pyrogen or placement in a steam cabinet; excessively prolonged exposure to a heat load with resultant "exhaustion" of temperature-regulating processes; and the loss of temperature regulation seen in association with severe brain damage and in moribund patients. It has been postulated that, except under circumstances such as these, an "emergency regulatory mechanism" in fever operates to prevent the elevation of body temperature to levels at which fever per se is life-threatening.

It is doubtful whether body temperatures in the range of 104°F (40.0°C) are harmful, even if prolonged for several days. Indeed, this is the temperature level found in...
athletes during hard exercise. Thus, the rationale for the administration of antipyretics is open to serious question, except in rare instances of severe hyperthermia and in patients in whom the increased circulatory demands imposed by fever may be undesirable; for example, children with myocardial disease. In the child who has a history of convulsions, the administration of an anticonvulsant during febrile illnesses is more rational and effective as a prophylactic measure against convulsions than the routine use of antipyretics, and it permits preservation of fever as a diagnostic and prognostic index.

DISADVANTAGES OF ANTIPYRETIC DRUGS

The potential disadvantages of the use of antipyretic drugs deserve consideration:

1) The temperature course can be a valuable diagnostic clue and an indicator of the severity or duration of illness, the adequacy of therapeutic response and the occurrence of complications or relapse. It is rather incongruous that we should be so hesitant about administering an analgesic to a patient with unexplained abdominal pain, but so willing to order an antipyretic for the patient whose only apparent abnormality at the moment is unexplained fever. After a diagnosis is established, fever may be the best, or the only, available sign for following the course of illness. For example, subsidence of fever is a valuable indicator of effectiveness of antibiotic therapy.

2) There is, of course, the previously mentioned possibility that fever may actually be a “friend” rather than an “enemy.” The possibility that body defenses are strengthened in the presence of fever has neither been proved nor refuted.

3) The fact that severe allergic or idiosyncratic reactions are relatively uncommon is little comfort to the patient who has one, or to his physician, particularly when indications for the use of the drug were questionable at best.

4) Where there are children, the mere presence of a potentially toxic substance (and this includes all antipyretics) invites disaster. Moreover, each time a drug is removed from its usual storage place, the likelihood that it will be ingested accidentally by a child is markedly increased. In recent studies on the epidemiology of accidental poisonings in childhood it was found that in the majority of instances of accidental ingestion of drugs by children, the material involved had been removed from its usual place of storage to be administered either to the child who ultimately ingested it or to another member of the family. Of course, there is the additional danger that therapeutic overdosage may occur despite (or because of) specific instructions from the physician.

5) Antipyresis is not the only therapeutic effect of antipyretic drugs and the additional effects may “mask” or suppress signs and symptoms which could be of diagnostic importance. Most antipyretic drugs are analgesics to a greater or lesser degree and can therefore prevent the occurrence of pain. Most antipyretic drugs also have antirheumatic properties and will prevent the development of such overt manifestations as arthritis in the patient with rheumatic fever, without altering the progression of carditis. For this reason, their use in the patient with unexplained fever, in whom rheumatic fever is a diagnostic possibility, is contraindicated until such time as this diagnosis is definitely confirmed or eliminated.

6) Finally, and perhaps most important, antipyretic therapy all too frequently is allowed to replace or delay efforts to establish a definitive diagnosis and institute specific treatment.

The foregoing was not intended to imply that sick children should not be made comfortable. Although there is considerable question whether fever per se is responsible for malaise, aches and pains, every physician has occasionally seen utter misery give way to relaxation and sleep upon the administration of an antipyretic to a febrile child. On the other hand, children often feel surprisingly well despite high fevers, and antipyretic therapy is employed
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more for the benefit of the parents or the physician than the child. Recent publicity has sensitized parents somewhat to the dangers of the indiscriminate use of drugs, and a word of explanation as to why treatment is being withheld will usually be accepted and respected.

OTHER MEASURES TO LOWER BODY TEMPERATURE

In the home care of the febrile child, much of what is done actually interferes with heat diffusion from the body and tends to elevate temperature further. Fever occurs because heat production exceeds heat loss; the latter being dependent primarily upon conduction, convection and evaporation. As the only factor which will diminish heat production is subsidence of the basic disease process, any other reduction of body temperature must come about through enhancement of heat loss.

The common practice of bundling the febrile child in heavy blankets interferes with heat loss through evaporation, conduction and convection. Excessively high environmental temperature interferes with heat loss by conduction; this can be corrected simply by cooling the sickroom sufficiently to promote heat loss without producing discomfort. Heat diffusion by convection and evaporation can be augmented by increasing the circulation of air about the patient. Excessive humidity of the air diminishes heat loss, because evaporation is dependent upon the moisture content, as well as the temperature, of the surrounding air. The importance of some of these environmental factors is illustrated in Figure 1. This graph shows the temperature course of an infant with pneumonia and diarrhea; she had only a mild temperature elevation until the temperature within the enclosure in which she was kept (a "Baby Haven") was allowed to rise by removal of the ice container. The enclosure itself interfered with heat loss by convection (which, in turn, would be expected to interfere to some extent with cooling by evaporation), and heat loss by conduction was diminished by allowing the environmental temperature to rise. This resulted in a gradual increase in body temperature to 104°F (40.0°C). Reducing the environmental temperature by replacing ice in the enclosure was sufficient alone to cause a rapid reduction in fever.

An additional factor which is of importance in determining heat diffusion is the degree of hydration of the patient. Every physician has observed children whose fevers diminished when adequate hydration was accomplished. It has been shown that heat loss through perspiration varies directly with the degree of hydration. Simple measures, such as those mentioned, will help to prevent the development of excessive fever and, furthermore, will increase the reliability of fever as a diagnostic and prognostic clue. Such steps are important even when antipyretic drugs are being used, as these compounds act through the central nervous system to reduce febrile temperatures by promoting heat loss. When it is deemed necessary to institute additional measures to reduce fever, cautious sponging with tepid water, together with gentle massage to promote cutaneous vasodilatation, offer certain advantages over the use of antipyretic drugs. The accidental poisoning danger is lessened. The possibility of toxic or idiosyncratic reactions and the effects of antipyretic drugs other than antipyresis are eliminated. Temperature control can be "titrated" more closely, and the temperature can be allowed to return to its natural levels at will in order to determine what course it is following.

SELECTION OF AN ANTIPYRETIC DRUG

As for antipyretic drugs, the most energetic promotion and the greatest obfuscation concerns various preparations of two compounds, salicylamide and N-acetyl-p-amino-phenol (acetaminophen), and the comparison of these preparations with acetylsalicylic acid (aspirin). Widely divergent claims have been made regarding comparative toxicities and antipyretic potencies. Much of the prevalent confusion has arisen
as the result of poorly controlled clinical experiments, attempts to compare animal studies from one laboratory to another, and efforts to extrapolate experience from one species of experimental animal to another or even to humans.

Table I presents data from published reports concerning the comparative oral toxicities for animals of salicylamide and aspirin. Only those studies which made simultaneous comparisons of the two drugs are summarized here. Each figure represents the ratio of the LD₅₀ for aspirin and salicylamide. A figure of one indicates that the oral toxicities of the two drugs were equal; a figure of greater than one indicates that salicylamide was more toxic than aspirin, and a figure of less than one that it was less toxic.

These data illustrate well the fallacy of inferring that a compound will have a particular toxicity in one species on the basis of its toxicity in another. In the experiments of Drebinger, for example, salicylamide was 83% as toxic as aspirin in rats, but was 64% more toxic than aspirin in the mouse. In the studies of Boxill the situation was reversed: salicylamide was more toxic than aspirin in rats, and less toxic in mice and guinea pigs. The greatest difference in the toxicities of the two compounds found in

**TABLE I**

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
<th>Mouse</th>
<th>Guinea Pig</th>
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<tr>
<td>Drebinger⁷</td>
<td>.83</td>
<td>1.04</td>
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<tr>
<td>Hart⁸</td>
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<td>Bavin¹⁰</td>
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<td>Carron¹¹</td>
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<td></td>
</tr>
<tr>
<td>Boxill¹²</td>
<td>1.46</td>
<td>.80†</td>
<td>.62</td>
</tr>
<tr>
<td>Matsumura¹²</td>
<td>.65</td>
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</table>

* Based on ratio of

<table>
<thead>
<tr>
<th>Aspirin</th>
<th>Salicylamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD₅₀:</td>
<td></td>
</tr>
</tbody>
</table>

(A figure of greater than one indicates that salicylamide was more toxic than aspirin and a figure of less than one that it was less toxic.)

† Fasted vs. ** non-fasted animals.
These studies were 64%, and in most instances the differences were much less. These data indicate that when salicylamide and aspirin are compared in the same laboratory under identical conditions, there appear to be no consistent or striking differences in their toxicities in experimental animals.

There are fewer data regarding the comparative oral toxicities of acetaminophen and aspirin in animals (Table II). Species differences are at least as striking here as in the evaluations of salicylamide toxicity. In the experiments of Boxill, acetaminophen was much less toxic than aspirin in rats and guinea pigs, and much more toxic in fasted mice, and the toxicities of the two compounds were essentially equal in mice that were not fasted.

In these and in the salicylamide studies, it is apparent that marked species differences preclude making even an intelligent guess as to the comparative toxicities of aspirin, salicylamide and acetaminophen in human beings. At the present time, there are not sufficient data regarding human cases of intoxication with the latter two compounds to permit direct estimations of comparative toxicities.

Intoxication either with salicylamide or acetaminophen differs markedly from intoxication with aspirin. The most striking feature is central nervous system depression, and death may occur as the result of respiratory failure. Hyperpnea does not occur, nor do the respiratory alkalosis and metabolic acidosis seen in salicylate intoxication. There is no specific antidote, and treatment is entirely symptomatic.

Claims regarding the comparative antipyretic potencies of salicylamide, acetaminophen and aspirin are conflicting. Figure 2 presents a comparison, adapted from the data of Boxill, of the effects of these three drugs in rats. The curves depict the differences in temperature from those found in untreated, febrile rats and therefore provide an estimate of the degree of temperature reduction which was achieved at varying intervals of time after the oral administration of the test drugs. In these experiments, both salicylamide and acetaminophen produced a more rapid fall in temperature than did aspirin. However, the temperature did not fall as far in salicylamide-treated animals and returned within 2 hours nearly to the levels seen in the febrile controls. Acetaminophen provoked essentially the same degree of temperature reduction as aspirin, but its effect was somewhat less prolonged.

These results agree well with those obtained by other workers10,12,14 although one investigator found no antipyretic effect of salicylamide in rabbits,15 even when twice the effective dose of aspirin was given. These data cannot, of course, be transposed directly to human subjects. However, the fact that the curves depicted here parallel the blood levels obtained with these compounds in human subjects10,17 suggests that similar curves of antipyretic effect might be expected.

In a recent report by Vigne18 on the antipyretic effectiveness of salicylamide in febrile infants, it was suggested that this compound and aspirin were equally effective. However, despite the fact that the dose of salicylamide used was twice as large as the dose of aspirin, the degree of antipyresis which was achieved was no greater, and actually may have been less.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Rat</th>
<th>Mouse</th>
<th>Guinea Pig</th>
</tr>
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<tr>
<td>Boxill16</td>
<td>.39</td>
<td>.05</td>
<td>.41</td>
<td>1.18**</td>
</tr>
</tbody>
</table>

* Based on ratio of

Aspirin

LD50:

Acetaminophen

(A figure of greater than one indicates that acetaminophen was more toxic than aspirin and a figure of less than one that it was less toxic.)

† Fasted vs. ** non-fasted animals.
HOURS AFTER DRUG

(Each drug given orally in a dose of 125mg/kg.)

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Fig. 2. Comparative antipyretic activities of aspirin (A), N-acetyl-p-aminophenol, acetaminophen (N) and salicylamide (S) in rats. Curves depict differences of temperature between treated and untreated febrile animals. Adapted from the data of Boxill.*

Colgan and Mintz* found that the antipyretic effects of acetaminophen and aspirin were essentially equivalent in febrile children, though the duration of action of acetaminophen was somewhat shorter than that of aspirin.

The foregoing suggest that aspirin and acetaminophen are closely comparable, while salicylamide is somewhat inferior, insofar as antipyretic effectiveness is concerned.

There are, of course, additional factors which should be considered and which have been brought forth in claims regarding these compounds. The fact that salicylamide, acetaminophen and a number of additional analgesic-antipyretic formulations are available as palatable liquids purportedly makes for greater acceptance and “accuracy of dosage.” Acceptability of any potentially-toxic material is a doubtful blessing. The more acceptable the material, the more likely that it will be ingested in potentially toxic amounts by a child. It seems far safer to make a drug palatable at the time it is administered (for example, by mixing it with honey or jam) than to invite disaster by storing it about the home disguised as candy or a tasty beverage. This remark applies as well to candied aspirin as to flavored liquid preparations. Aspirin actually is not so unacceptable to children as to warrant its substitution by other preparations or the addition of flavoring, for reasons of acceptability alone.

At least in the home care of children, accuracy of dosage is a highly overrated factor. It is certain that, if the material in question were being injected from a syringe or instilled directly from a pipette into the child’s stomach, a liquid preparation could be handled with much greater accuracy. However, this difference largely disappears when the drug is measured in units of teaspoonful or approximate fractions thereof, and an unknown amount is dispensed down the child’s chin. Furthermore, when antipyretic drugs are used properly, the therapeutc dose is so far removed from the toxic dose that a high degree of accuracy is not necessary.

Salicylamide and acetaminophen are not
salicylates and are not converted to salicylate in the body. Consequently, these compounds can be used in patients who are sensitive to aspirin.

Aside from the latter point, there appear to be no highly cogent reasons for selecting one of these newer antipyretics over one which may have stood the physician in good stead in the past. This statement is meant not to champion the cause of older preparations, but rather to inject what seems to be an appropriate attitude of reasonable-ness into a problem which for many has been perplexing indeed.

REFERENCES
USES AND ABUSES OF ANTIPYRETIC THERAPY

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