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CLINICAL PHARMACOKINETICS OF SALICYLATES: A RE-ASSESSMENT

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1 Aspirin is partly hydrolyzed to salicylic acid during absorption. Absorbed aspirin is rapidly hydrolyzed systemically. Salicylic acid elimination kinetics are dependent on drug concentration due to the limited capacity of two major biotransformation pathways: formation of salicyluric acid and of salicylphenolic glucuronide.

2 The time courses of the various pharmacological effects of single doses of aspirin are not directly coincident with the plasma concentrations of either aspirin or salicylic acid but there is reasonably good evidence that the pharmacological effects are related to the concentration of aspirin, salicylic acid, or both.

3 Steady-state plasma salicylate concentrations increase more than proportionally with increasing daily dose; the time required to reach steady state increases with increasing daily dose. Dosage intervals of 8 or even 12 h are usually sufficient to maintain plasma salicylate concentrations in the anti-inflammatory concentration range. Monitoring of plasma salicylate concentrations in this range is facilitated by the relatively small drug concentration fluctuations during a dosing interval at steady-state.

4 Limited data suggest that the pharmacological activity of salicylate is produced by free (unbound) drug. As the plasma protein binding of salicylic acid is concentration-dependent and subject to pronounced interindividual differences, it is preferable, at least in principle, to monitor free rather than total concentrations of salicylate in plasma. Although salicylate concentration in saliva reflects the free rather than total salicylate concentration in plasma or serum, use of saliva for indirect monitoring of plasma salicylate concentrations seems to be impractical for technical reasons.

Introduction

THE pharmacokinetics of aspirin and salicylic acid in man are now reasonably well characterized and the pertinent information has been summarized in recent reviews (Levy, 1975; 1978; 1979). This article is therefore devoted primarily to a re-assessment of some clinically important aspects of salicylate pharmacokinetics against the background of some old and some new information about the subject.

Aspirin compared with salicylic acid

A considerable fraction of an oral dose of aspirin is hydrolyzed presystemically; the rest is hydrolyzed rapidly ($t_{\frac{1}{2}} \simeq 15$ min) after absorption. As this hydrolysis is an enzymic process, there is the likely possibility that 'first-pass' hydrolysis of the drug (during which the intestinal and hepatic tissues are exposed to relatively high concentrations of aspirin) is capacity-limited and absorption site-dependent. The importance of this issue depends on whether there are significant clinical pharmacological differences between aspirin and its hydrolysis product salicylic acid.

Unfortunately, comparative clinical studies of aspirin and salicylic acid or its salts have been few. It seems that sodium salicylate has only about 60% of the antipyretic potency of aspirin, on a molar basis (Seed, 1965). It has also been stated that aspirin is a better analgesic than is sodium salicylate (Lasagna, 1961) but the actual data have never been published. The antiplatelet effect of aspirin seems to be attributable to acetylation of an enzyme involved in platelet aggregation (Pearson, 1978) and is not produced by salicylic acid. On the other hand, the anti-inflammatory activity of a salt of salicylic acid seems to be as good as that of aspirin in patients with rheumatoid arthritis (Blechman & Lechner, 1979).

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Pharmacokinetic aspects of the analgesic effect of aspirin

A number of investigators have demonstrated that the analgesic effect of aspirin in man increases with increasing dose up to single doses of at least 1200 mg (Murray, 1964; Parkhouse, Rees-Lewis, Skolinik & Peters, 1968; Seki, 1978). A dose-response relationship has also been demonstrated with respect to the quantitative effect of aspirin on the electroencephalogram of normal volunteers (Pfeiffer, Goldstein, Murphree & Hopkins, 1967). This dose-response relationship should more appropriately be considered as a relationship between drug concentration and response because receptors 'see' a concentration of drug molecules and not a number of tablets or capsules. Nevertheless, a relationship between aspirin or salicylate concentration and intensity of analgesic effect has been denied by many investigators and authors, simply because the time courses of drug concentrations and intensity of analgesia do not coincide. That lack of coincidence reflects a lack of a simple and direct relationship, but not necessarily of a relationship *per se*.

As has been explained elsewhere (Levy, 1973), a delay in the time of occurrence of a maximum pharmacological effect, relative to the time of occurrence of the maximum concentration of a drug in plasma, can be due to several reasons. For example, the site of drug action may have the pharmacokinetic characteristics of a compartment distinct from the body's apparent central compartment (which includes the plasma phase), the drug may act indirectly, or the drug's effect may be mediated by an active metabolite. In these instances, there does indeed exist a concentration-effect relationship but it will be complex and it may be time-dependent.

Some 20 years ago I reviewed the results of many reported studies of the temporal pattern of pain relief produced by a number of analgesics. Contrary to expectations based on pharmacokinetic theory (Levy, 1967), the analgesic effect of all these agents as well as of the placebos declined at essentially the same rate. The relevant evidence was reviewed in greater detail several years later (Levy, 1973) and has been strengthened by additional studies since that time. I concluded that "in the case of analgesics the rate of decline of pharmacologic activity is not specific to the analgesic agent but specific to the effect elicited, namely, that of analgesia" (Levy, 1961). With a greater measure of creative introspection, this conclusion should even then have led to the hypothesis that analgesics as well as placebos trigger the release or activation of an endogenous analgesic agent, the activity of which (and the decline in concentration of which with time?) is reflected by the time course of analgesia elicited after administration of clinically effective analgesics and placebos.

Why then is there a dose dependence of clinical analgesia? Presumably, the larger the dose or the higher the maximum drug concentration at its site of action, the more endogenous analgesic is activated or released. The greater the maximum analgesic effect, the longer is the duration of effect and the greater is the total effect (area under effect against time curve). By that reasoning, sustained release aspirin preparations are unlikely to provide prolonged analgesia. In fact, the duration of analgesic activity produced by regular and sustained release aspirin has been found to be essentially identical (Cass & Frederik, 1965*a*). On the other hand, rapidly absorbed aspirin preparations should produce not only earlier but also more pronounced analgesic effects than those produced by more slowly absorbed aspirin dosage forms. That would be expected particularly if aspirin is more effective than salicylic acid. The much shorter biological half-life of the former results in a more pronounced effect of absorption rate on peak aspirin than on peak salicylic acid concentrations in plasma (Levy, 1965).

Salicylic acid, but not aspirin accumulates in plasma during repeated drug administration. Specifically, peak plasma salicylate concentrations after each dose of aspirin increase gradually until a steady-state is reached. Aspirin concentrations decline to essentially zero during the usual dosing interval due to the short biological half-life of the drug. One might expect to see gradually increasing analgesic effects during repeated aspirin administration if analgesia is due to salicylic acid, and no such increase if the analgesic effect is produced primarily by aspirin itself. The data of Gruber *et al.* (1979) show little if any increase in analgesic effect of a second 650 mg dose of aspirin administered to post-partum patients 4 h after the first dose. Cass & Frederik (1965*b*) have found that the analgesic effect of aspirin in male patients with chronic pain is essentially constant during 6 d of drug administration. These investigators observed a slight increase in analgesic effect of aspirin with time during 6 d of drug administration. Though certainly not definitive, most of these observations are largely consistent with the assumption that the analgesic effect of aspirin is produced primarily by that drug rather than by its hydrolysis product salicylic acid. It must be appreciated, however, that little is known about the dynamics of repeated doses of analgesics — most analgesimetric studies have been done with single doses — and the analysis presented here is at best a preliminary one, based on the limited data available.

It is appropriate, despite the limited clinical data base, to consider the pharmacokinetic factors affecting aspirin rather than salicylic acid concentrations in plasma after oral administration of aspirin. Rowland *et al.* (1972) have found that 28–35% of an oral dose of aspirin 650 mg in aqueous

solution is hydrolyzed during absorption in man. Studies in dogs have shown that this hydrolysis occurs in the gut wall as well as in the liver and that there is no apparent saturation of hepatic hydrolysis or extraction over a limited dose range (250–500 mg per dog weighing 18–23 kg) (Harris & Riegelman, 1969).

In man, administration of aspirin tablets with food reduces maximum aspirin concentrations to about one-half of the maximum concentration achieved when the drug is administered with 250 ml water on an empty stomach but food has no statistically significant effect on the amount of aspirin absorbed intact, as reflected by the area under the concentration-time curve (Koch *et al.*, 1978). The area values obtained in that study are similar to those reported by Rowland *et al.* (1972) but the aspirin bioavailability estimates are much lower (5–18%). The difference seems to be due to problems of pharmacokinetic analysis in the study of Koch *et al.* (1978), who did not give the drug intravenously and who therefore could not use a direct comparison of area values obtained by oral and intravenous doses of aspirin to estimate the extent of presystemic hydrolysis.

There seem to be pronounced and consistent interindividual differences in the presystemic hydrolysis of orally administered aspirin. Hollister (1972) has determined the serum concentrations of aspirin after oral administration of 1300 mg in two rapidly absorbed tablet dosage forms to 12 adult subjects. Examination of the individual data (kindly made available by Dr Hollister) has revealed a four-fold range of areas under the concentration-time curve, with a strong correlation between area values for each subject ($r=0.825$; $P<0.001$). Thus, there are those who consistently exhibit very pronounced presystemic hydrolysis of orally administered aspirin and others who consistently show much less hydrolysis of the drug during absorption. It would be interesting to determine if the analgesic effect of aspirin is smaller in the former than in the latter type of individual.

Kinetics of salicylate elimination

Salicylic acid, the hydrolysis product of aspirin, seems to be responsible for the drug's anti-inflammatory and toxic effects. Salicylic acid is eliminated by formation of salicyluric acid (the glycine conjugate of salicylic acid), salicylphenolic glucuronide, salicylacyl glucuronide, gentisic acid, and by renal excretion of salicylic acid as such. The first two of these products are formed by capacity limited processes (Michaelis-Menten kinetics) with *in vivo* K_M values well below the therapeutic concentration range of the drug (Levy, Tsuchiya & Amsel, 1972). Consequently, steady-state plasma salicylate concentrations increase much more than proportionately with increasing daily dose of the drug and the time required to attain steady-state increases with increasing dose (Levy & Tsuchiya, 1972). This disproportionality is more pronounced with respect to free (unbound) than total (free plus bound) plasma concentrations (Aarons, Bochner & Rowland, 1977; Furst, Tozer & Melmon, 1979), due to the decreased plasma protein binding of salicylic acid with increasing concentrations.

As a consequence of the capacity-limited kinetics of salicylate elimination, plasma salicylate concentrations decline relatively more slowly with increasing daily dose or concentration. Based on a pharmacokinetic analysis of this phenomenon, Levy & Giacomini (1978) have predicted that adequate plasma salicylate concentrations for anti-inflammatory therapy can be maintained by administering the drug only every 8 or 12 h rather than every 4–6 hours. This prediction has now been confirmed by several groups of investigators with respect to children (Mäkelä, Yrjänä & Mattila, 1979; Pachman, Olufs, Procknal & Levy, 1979) and adults (Cassell, Furst, Dromgoole & Paulus, 1979; Bensen, Laskin, Paton, Little & Fam, 1979; Cohen, Thomas & Cohen, 1978). It is important, however, that the large single doses of a salicylate required for a two or three times daily dosage regimen be administered in a form that minimizes gastric irritation. Moreover, it has been suggested on the basis of retrospective drug surveillance studies that administration of larger doses of aspirin at longer intervals of time causes a higher incidence of deafness than administration of similar daily doses at more frequent intervals (Miller, 1978). This is a reasonable possibility in principle but seems unlikely in practice. The maximum plasma salicylate concentrations produced by either an 8- or a 12-hourly dosing regimen (same daily dose individually adjusted to achieve timed average concentrations of about 23 mg per 100 ml) were 27.9 and 30.8 mg per 100 ml, respectively, in one very well controlled study (Cassell, Furst, Dromgoole & Paulus, 1979). Peak concentration differences between a 6- and 8-hourly dosage regimen are also rather small in the anti-inflammatory dose range (Levy & Giacomini, 1978). A rigorous prospective clinical trial will be required to assess this problem definitively.

Implications for pharmacokinetic monitoring

Although controlled clinical studies of the relationship between plasma salicylate concentration and anti-inflammatory effect have apparently not been published, there is a recent report in abstract that

serum salicylate concentrations of between 20 and 30 mg per 100 ml produce the best clinical response in patients with juvenile rheumatoid arthritis (Doughty, Giesecke & Athreya, 1979). On the other hand, there is a high incidence of systemic adverse effects at salicylate concentrations above 30 mg per 100 ml (Mäkelä, Yrjänä & Mattila, 1979). Thus, the therapeutic concentration range of salicylate is quite narrow. For this reason and because of pronounced interindividual differences in the elimination kinetics of the drug, dosage must be individualized on the basis of plasma concentration monitoring and clinical assessment of the individual patient. The usefulness of such monitoring has already been demonstrated (Bardare, Cislaghi, Mandelli & Sereni, 1978).

The strategies for the pharmacokinetic control and clinical interpretation of steady-state concentrations of drugs in blood, plasma or serum have been reviewed previously (Levy, 1974). When these concentrations fluctuate appreciably during a dosing interval due to absorption, distribution and elimination of the drug, it becomes necessary to draw several blood samples during a dosing interval or (and this is much less desirable) to obtain one sample that is rigorously timed relative to the time of administration of the preceding dose. Fortunately, such precaution is usually not required in the case of salicylates because the plasma concentration of this drug does not change very much during dosing intervals of up to 8 h at average plasma salicylate concentrations of 20 mg per 100 ml or above. In one study of children with juvenile rheumatoid arthritis, the ratio of maximum to minimum (peak to trough) concentrations was less than 1.3 during an 8 h dosing interval at time averaged salicylate concentrations of 20 mg per 100 ml or above (Pachman, Olufs, Procknal & Levy, 1979).

It is a generally accepted concept that free rather than protein bound drug is pharmacologically active. There is evidence from animal studies that this concept applies to salicylic acid (Reynolds & Cluff, 1960). As plasma protein binding of salicylate is concentration dependent, variable between individuals and affected by disease (evidence reviewed by Levy, Procknal, Olufs & Pachman, 1980), it is preferable in principle to monitor free rather than total salicylate concentrations in plasma or serum. However, determination of free drug in these fluids is time-consuming and costly, and therefore not suitable for routine clinical use with presently available methods. One possible alternative is the monitoring of salicylate concentrations in saliva, as salivary drug concentrations usually reflect free rather than total drug concentrations in plasma or serum.

The utility of salivary salicylate determinations as a convenient and non-invasive indirect means of monitoring free salicylate concentrations in serum has recently been explored in a group of children with juvenile rheumatoid arthritis (Levy *et al.*, 1980). Although a very strong linear correlation between salicylate concentration in saliva and free salicylate concentration in serum could be demonstrated, inter- and intraindividual variations in the saliva : serum drug concentration ratio are considered sufficiently large to limit the clinical usefulness of the procedure.

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DR AXELSEN pointed out that there was a difference between therapeutic use and intoxication. In the latter, patients and animals who were acidotic with a low blood *p*H had a higher concentration of salicylate in brain and other tissues, which could be important in the context of lethality.

DR BRUNE agreed and added that *p*H and diffusion of unbound drug into the brain could also be important for the antipyretic activity of salicylates.

In response to a question from Professor Segre, Dr Brune said that in his opinion the anti-inflammatory and most of the analgesic activity of acidic drugs were peripheral. However, autoradiography revealed that non-acidic drugs reached high concentrations in the brain, and he could not be certain that they did not mediate some analgesic action there. He emphasized that where the concentration of acidic drugs in plasma was increasing and binding to plasma proteins decreasing because of saturation of the binding sites, that central nervous system effects could be expected. This was true also for phenylbutazone and the highly lipophilic indomethacin. Even in the ionized state the latter could reach brain in concentrations producing central side-effects.

PROFESSOR SZCZEKLIK asked whether there was evidence from autoradiographic studies that aspirin

affected megakaryocytes lying in bone marrow as well as circulating platelets.

DR BRUNE said that in the autoradiographic study reported he used a tritium label in the acetyl moiety, and in this particular situation there was a visible degree of labelling detected in the bone marrow compartment. He pointed out that aspirin acetylates cyclo-oxygenase, and speculated that it would occur in megakaryocytes, although there was at present no proof.

PROFESSOR KRONEBERG questioned the significance of the accumulation of aminopyrine in bone marrow, particularly in the context of agranulocytosis, which most people regarded as an allergic process.

DR BRUNE speculatively replied that if there were accumulation of aminopyrine in lymphocytes and there was accumulation in spleen and thymus tissue, it could accompany the sensitization which preceded allergic bone marrow damage.