Indomethacin serum concentrations in man

Effects of dosage, food, and antacid

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Emori, H. W., Paulus, H., Bluestone, R., Champion, G. D., and Pearson, C. (1976). *Annals of the Rheumatic Diseases*, 35, 333–338. Indomethacin serum concentrations in man. Effects of dosage, food, and antacid. In the use of anti-inflammatory compounds, sustained serum levels are thought to be related to drug efficacy. This study shows that frequent clinical administration of indomethacin can result in sustained serum levels of the drug and that food and antacid may have important modifying effects on serum indomethacin concentrations. After oral ingestion by fasting subjects, indomethacin rapidly appeared in the serum, usually reaching peak concentrations in 30 to 90 minutes. Food delayed and decreased the mean peak level; antacid delayed the peak and slightly enhanced subsequent concentrations. With multiple dose schedules plateau levels were reached after 24 hours. When a total daily dose of 150 mg was given as 25 mg every 4 hours peak concentrations were the same but fluctuations were smaller and average concentrations were higher than with a dosage of 50 mg every 8 hours.

Indomethacin (a 3-indolyl acetic acid derivative) is a widely used drug. Although its anti-inflammatory activity in animal models is exceptionally potent, its efficacy in rheumatoid arthritis has been controversial (Cooperating Clinics Committee of the American Rheumatism Association, 1967; O'Brien, 1967). Reports on its metabolism (Duggan and others, 1972), plasma concentrations (Caruso, 1971), serum and synovial fluid pharmacokinetics (Emori and others, 1973), and its interaction with salicylates (Lindquist and others, 1973; Van Arman, Nuss, and Risley, 1973) have considerably broadened our knowledge of its usage. A better understanding of factors affecting its serum drug levels, coupled with an assumption that blood and tissue levels of the drug are important in drug therapy, may lead to more effective and less toxic use of indomethacin in clinical medicine.

Using a protocol designed to simulate the clinical application of the drug, we studied the serum concentrations of indomethacin in normal volunteers and in patients with rheumatic disorders in order to evaluate the range of individual and inter-subject responses to various clinically practical dosages and schedules of the drug. Because anti-inflammatory drugs are usually given with meals or

antacids in order to avoid gastric side effects, we evaluated the effects of these variables on serum drug levels.

Methods

SINGLE DOSE STUDIES

After initial clinical evaluation to exclude gastrointestinal haematological, and renal disease, 8 fully informed, consenting, healthy adult male volunteers (33–55 years of age, mean 40 years) were admitted to an 8-week trial. At weekly intervals the dosage schedules shown in Table I were given to determine individual and intersubject responses to the same (50 mg), larger (75 mg), and smaller (25 mg) single oral doses of indomethacin, and to evaluate

Table I Eight normal volunteers given drug at 8 a.m. after an 8-hour fast

Study week	Indomethacin dosage
1	50 mg
2	50 mg
3	50 mg
4	25 mg
5	75 mg
6	50 mg
	30 mg MgALOH gel

the effects of concurrent administration of magnesium-aluminium hydroxide gel* on serum concentrations after single doses of indomethacin. The order of administration of schedules 2 to 8 was randomized. Each time serial 15 ml blood samples were taken after ingestion of the drug dose.

In order to evaluate the later course of serum levels 4 outpatients with rheumatoid arthritis (ages 42–70) were requested to stop all medication for 24 hours. After an 8-hour fast, 50 mg oral indomethacin was given and serum specimens obtained during the next 9 hours. 4 subjects (2 males, 2 females; ages 26–28) were given a single 100 mg oral dose after an 8-hour fast to determine peak serum levels. Blood samples were taken at intervals for up to 7½ hours after the dose.

MULTIPLE DOSE STUDIES

Six consenting males (ages 26–62, mean 45 years), in hospital for treatment of their arthritis (4 rheumatoid arthritis, 2 degenerative joint disease), were studied to evaluate the effects of several dosage schedules on serum drug concentrations during indomethacin therapy. They were initially screened to exclude gastrointestinal, haematological, hepatic, or renal disease. Anti-inflammatory drugs were not used during the 2 weeks before hospitalization. Drug administration was carefully controlled. Serum concentrations after single 25 and 50 mg oral doses of indomethacin, given in the fasting state, were first determined in each subject; a 7-day interval elapsed between these doses. 24 hours after the second fasting dose treatment was begun with 150 mg indomethacin daily for 4 days. Subjects were randomly assigned to take either 25 mg every 4 hours or 50 mg every 8 hours with a meal or a substantial snack consisting of 341 ml (12 ounces) of milk and two salted biscuits. Multiple samples of venous blood were obtained after the initial dose to determine the response to a single dose given with food, and after the doses taken with breakfast on the second and fourth days to assess the cumulative effects of multiple doses. Drug administrations were then discontinued for 30 hours; when resumed, the randomization was reversed so that each subject would experience both dosage schedules (to permit comparison of the two schedules).

A third variation, also with a total daily dose of 150 mg indomethacin, was then evaluated by giving 25 mg every 4 hours during the waking hours and 50 mg at bedtime for 4 days. Bedtime doses were always given with 30 ml magnesium aluminium hydroxide gel (MgALOH gel). Blood specimens were collected 8 hours later to evaluate the effectiveness of these schedules in maintaining serum concentrations during sleep.

ASSAY METHOD

Specimens were centrifuged at the end of each trial day and the serum collected and frozen at -4°C until analysed within 2 months. Previous studies have shown no change in serum indomethacin concentrations during 4 months of storage at -4°C . Indomethacin assays were performed using a modification (J. E. Baer, personal communication, 1970) of a spectrofluorometric method after Na_2CO_3 extraction (Hucker and others, 1966). In this method, 3 ml of sample are buffered with 2 ml 0.5 mol/l, pH 5 citrate;

the indomethacin is then extracted with 25 ml of a solution containing fluorescence-free heptane (97%) and amyl alcohol (3%). The heptane phase is washed twice with an equal volume of citrate buffer. A 15 ml aliquot of the washed heptane phase is alkalized with 4 ml 0.2 mol/l Na_2CO_3 to extract the drug. The aqueous phase after centrifugation is removed for fluorescence intensity measurement. Occasionally further centrifugation is required because of turbidity in the aqueous phase at this point. The clear aqueous phase is read in an Aminco SPF spectrofluorometer at excitation wave length 295 nm and emission is measured at wave length 375 nm in quartz cuvettes. A water blank and two serum standards containing 2.5 and 5.0 $\mu\text{g}/\text{ml}$ were analysed with each set of determinations. Repeated assays of standards, using fresh drugs at weekly intervals, were accurate to 0.08 $\mu\text{g}/\text{ml}$ (SEM 0.003). When 5 $\mu\text{g}/\text{ml}$ of desmethyl indomethacin, an inactive metabolic product of indomethacin, was added to 2.5 $\mu\text{g}/\text{ml}$ of indomethacin in serum, apparent indomethacin levels were $2.66 \pm 0.07 \mu\text{g}/\text{ml}$ on three trials. In earlier studies by our laboratory, no interference in the spectrofluorometric reading of known indomethacin concentrations occurred when 0.3 mg/ml of sodium salicylate was added to serum specimens (Champion and others, 1972).

Results

SINGLE DOSE STUDIES

Serum levels after administration of 50 mg indomethacin to 8 healthy fasting volunteers on 3 separate occasions at weekly intervals (24 trials) are shown in Fig. 1 in which mean values ($\pm$ SE) are plotted. The peak concentration of $2.19 \pm 0.20 \mu\text{g}/\text{ml}$ occurred 60 minutes after drug ingestion. After reaching peak concentrations serum levels fell rapidly during the next 3 hours (mean $T_{1/2}$ for the interval between 60 and 240 minutes after the dose was 90 minutes) so that the mean concentration 5

FIG. 1 Serum concentrations after 25 mg, 50 mg, and 75 mg indomethacin to 8 fasting healthy volunteers and 100 mg to 4 healthy fasting volunteers. Mean $\pm$ SE

* Maalox, William H. Rorer, Inc.

Table II Indomethacin blood levels ($\mu\text{g/ml}$) after 50 mg to 8 fasting volunteers at weekly intervals

	Case No.									
Week	1	2	3	4	5	6	7	8	Mean	SEM
Peak concentrations										
1	0.75	1.90	3.10	1.15	3.10	4.95	3.55	2.00	2.56	0.49
2	0.50	3.20	4.70	2.60	3.25	2.30	3.70	2.05	2.79	0.44
3	2.50	3.10	3.11	2.30	3.75	3.75	3.05	2.90	3.05	0.20
Individual mean	1.25	2.75	3.64	2.02	3.37	3.67	3.43	2.32	2.80	
5-hour concentrations										
1	0.50	0.55	0.30	0.45	0.30	0.37	0.30	0.75	0.44	0.06
2	ND	0.65	0.30	0.30	0.27	0.45	0.30	0.50	0.40	0.05
3	0.55	0.63	0.33	0.35	0.30	0.60	0.35	0.95	0.51	0.19
Individual mean	0.53	0.61	0.31	0.37	0.29	0.47	0.32	0.73	0.45	

ND = not done.

hours after drug ingestion was $0.48 \pm 0.01 \mu\text{g/ml}$. A sixfold variation in peak concentration was noted between individuals; individual peak levels occurred between 60 and 210 minutes after drug ingestion. Mean peak levels on each of the 3 occasions were comparable and occurred at 60 minutes after drug ingestion. Peak levels for individuals receiving weekly dosages varied markedly, although with one exception serum levels after 5 hours were remarkably constant from week to week (Table II).

In 6 fasting males 50 mg indomethacin produced a serum concentration curve similar to that seen in normal healthy adults except for a slightly but insignificant greater mean peak level (Fig. 2). Serum levels at 5 hours after drug ingestion were comparable to serum levels in normal volunteers. Serum levels of 4 patients evaluated for 9 hours after a 50 mg dose were almost identical to those seen in the previous patients during the first 5 hours. However, after the initial rapid decline from peak concentrations, there was a gradual decline in serum levels (Fig. 2).

FIG. 2 Serum concentrations after 25 mg and 50 mg indomethacin to 8 fasting healthy normals and to 10 (6 hospitalized, 4 clinic) fasting patients with rheumatic complaints. Mean $\pm$ SE

When a 25 mg dose was given to the 8 healthy volunteers the mean peak level occurred at 30 minutes and was approximately half that of the peak after the 50 mg dose to the same volunteers. The $T_{1/2}$ for the interval between 60 and 240 minutes after the dose was 140 minutes (Fig. 1). In the patients 25 mg of the drug produced a mean peak serum level that was approximately twice that in the normal volunteers. The difference between peak values for normals and patients was not statistically significant because of marked individual variabilities in both groups. Serum levels 5 hours after drug ingestion were comparable in both groups (Fig. 2).

The 75 mg dose was studied only in the 8 normal volunteers. The mean peak serum level occurred after 60 minutes and was twice that after the 50 mg dose. The decline after peak concentrations was more rapid ($T_{1/2}$ between 60 and 240 minutes was 37 minutes), and 5 hours after drug ingestion the mean serum concentration was approximately equal to that seen after both smaller doses (Fig. 1).

A 100 mg dose given to 4 normal volunteers (described above) showed a somewhat delayed peak (2 hours after drug) that was three times the peak after the 50 mg dose to the 8 healthy volunteers (Fig. 1). The $T_{1/2}$ after the occurrence of the mean peak level was 30 minutes as measured between 60 and 240 minutes after the dose. One subject was followed for $7\frac{1}{2}$ hours, the other 3 for $1\frac{3}{4}$ to 3 hours.

The addition of 30 ml MgALOH gel to a 50 mg dose delayed the occurrence of the mean peak concentration and slightly increased subsequent concentrations without decreasing the rate of decline of serum concentrations (Fig. 3).

In 6 hospitalized patients administration of indomethacin (both 25 mg and 50 mg) with a standard hospital breakfast resulted in a delayed and decreased mean peak serum level when compared with the same doses given to fasting subjects. Serum

levels 6 hours after the 25 mg dose and 8 hours after the 50 mg dose were similar to those at comparable times after fasting administration (Fig. 3).

FIG. 3 Serum concentrations after 50 mg indomethacin; MgALOH gel 30 ml; and a standard hospital (VA) breakfast (6 patients). Mean $\pm$ SE

MULTIPLE DOSE SCHEDULES (FIG. 4)

After the fourth dose (day 2) 50 mg indomethacin given every 8 hours with a meal or snack produced a concentration curve with a mean peak level of 1.48 ± 0.31 μ g/ml occurring 90 minutes after drug administration. A clear-cut biphasic removal pattern was not apparent as after the fasting doses of indomethacin alone, perhaps because fewer time-points were assayed. 8 hours after drug ingestion serum levels were roughly 30% greater than serum levels after a single 50 mg fasting dose. The serum concentration curve after the 10th dose (on day 4) of continuous therapy was almost identical to that described above after the fourth dose.

When 25 mg of the drug was given every 4 hours with a meal or substantial snack, peak serum levels were very similar to peak levels after the repeated 50 mg doses (as measured on day 2). However, mean serum levels $3\frac{1}{2}$ hours later were twice that of the minimum serum levels observed before the next 50 mg dose on the every 8-hour schedule. On day 4 the serum concentration curve for a dose of 25 mg every 4 hours also remained unchanged.

SIDE EFFECTS

Patients complained less than normal volunteers of

unfavourable side effects, the major complaint of the normal volunteers (9 of 12) being an ill-defined feeling of 'muzziness'. None complained of gastrointestinal symptoms. The patients, although specifically asked, did not complain of drowsiness. 3 of 10 patients did complain of slight epigastric discomfort, noted after a week of therapy on the multiple dose schedule.

Discussion

This study is based on the assumption that side effects and toxicity are more closely related to serum drug levels than to dosage in drugs with rapidly reversible effects. Although this assumption has been proved true for only a small number of drugs, it is generally accepted. In addition, the importance of sustained serum and tissue levels of a drug for maximum effectiveness has also been emphasized (Koch-Weser, 1972; Hvidberg, Lausen, and Jansen, 1972). Studies of the absorption, distribution, metabolism, and excretion of drugs are usually based on observations after a single dose to a small number of healthy subjects. Unfortunately, extrapolation of the findings of single dose pharmacokinetic studies into the clinical setting of chronic anti-inflammatory therapy is rarely successful because of many conflicting factors that may affect serum drug levels. Even within the controlled setting of a pharmacokinetic study, marked individual variations in drug concentrations are noted and cannot be predicted in advance. Therefore, this study was not designed to explore the usual pharmacokinetic parameters, nor to develop a computer model based on single dose observations in a few subjects, but rather was designed to observe directly the effects of several common clinical variables on serum concentrations.

In clinical practice indomethacin is often given in divided doses at 8- or 12-hour intervals. Because of the frequent association of anti-inflammatory drugs with symptoms of gastric irritation, it is usually given postprandially or with antacids. This study shows that frequency of administration, dosage, food, and antacids have important modifying effects on serum indomethacin concentrations.

FIG. 4 Serum concentrations during treatment of 6 patients with 150 mg indomethacin daily. Day 1 shows concentrations after initial dose of 25 or 50 mg. Days 2 and 4 show concentrations during a multiple dose schedule of 25 mg every 4 hours or 50 mg every 8 hours with food. Mean $\pm$ SE

Indomethacin rapidly appears in the serum after oral administration of the drug. Peak serum levels occur in 30–90 minutes, and increase with increasing single doses of the drug. After the peak there is a rapid decline of serum concentrations during the next 3 hours followed by a much slower rate of decrease in serum concentrations (between 5 and 9 hours after the dose). In a previous study (Emori and others, 1973) we found that indomethacin concentrations in synovial fluid approximate those in the serum during this later phase (between 5 and 9 hours after the dose). The kinetics in the first 3 hours after the dose are complex, and are influenced by drug absorption, distribution, and excretion. However, during the subsequent slower disappearance of indomethacin from the serum (and synovial fluid), it appears that the drug is re-entering the serum from tissue stores, is being metabolized, and excreted. These findings support Duggan's suggestion of an initial distributive phase from the vascular to the extravascular compartment and a subsequent phase of metabolism and re-entry of the drug from tissue stores (Duggan and others, 1972). Food delayed and decreased the mean peak level. Antacid delayed the peak and slightly enhanced subsequent concentrations. Antacids have been shown to have no effect upon (Lansdown and Radzin, 1963) nor depress or enhance (Hurwitz, 1971) the absorption and subsequent blood levels of orally ingested drugs. These effects have been explained by 'physiochemical' changes in the drug, or by physiological changes in the subject, caused by antacid ingestion (Rosenoer and Gill, 1972).

Both multiple dose schedules (150 mg daily in 3 or

6 divided doses) showed a cumulative effect by day 2, but without further increase in serum levels when remeasured on day 4. The smaller, more frequent 25 mg doses resulted in peak concentrations equal to those after the larger, less frequent 50 mg doses, but with much smaller fluctuations in serum concentrations. This smaller amplitude of fluctuations resulted in a greater mean serum concentration with the more frequent 25 mg doses.

The effects of some important factors of clinical administration of indomethacin have been measured, but the great individual variability in serum drug levels and of other factors not measured preclude accurate prediction of drug levels after a given dose(s) to an individual. For accurate dosage adjustment in individual patients it will be necessary to measure drug concentrations during therapy rather than attempt to extrapolate these data. However, if the anti-inflammatory efficacy and toxicity of indomethacin are related to sustained tissue concentrations of the drug rather than to brief peak serum levels, relatively stable indomethacin levels can be maintained during chronic therapy by the use of frequent small doses of the drug. Fluctuations in serum levels can be further decreased by administration with meals or antacid.

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