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NOTES

Choline Magnesium Trisalicylate: Comparative Pharmacokinetic Study of Once-Daily and Twice-Daily Dosages

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Abstract □ This randomized crossover study compared the pharmacokinetics of choline magnesium trisalicylate tablets administered once daily (3000 mg of salicylate) or twice daily (1500 mg of salicylate) for six d. Serum salicylate levels were measured by HPLC. Mean "trough" concentrations fell within the therapeutic range (5–30 mg/dL) with either regimen and were relatively constant, indicating that the steady state had been reached. The 24-h area under the salicylate curve ($AUC_{0-24\ h}$) after the final 3000-mg salicylate dose averaged about twice the mean 12-h AUC after the last 1500-mg dose, indicating that the two dosing regimens were equally bioavailable. Clinical observations and results of laboratory safety studies indicate that both dosage schedules of the drug are well tolerated. The present findings support the once-daily therapeutic use of choline magnesium trisalicylate.

Keyphrases □ Choline magnesium trisalicylate—pharmacokinetic comparison of once-daily and twice-daily dosages, humans □ Bioavailability—choline magnesium trisalicylate, once-daily and twice-daily dosage schedules, humans □ Pharmacokinetics—choline magnesium trisalicylate bioavailability after once-daily and twice-daily dosages, humans

Complexity of dosage schedule may cause nonadherence to self-administered drug regimens (1, 2), particularly among ambulatory, fully active patients. Conversely, simplicity of treatment, as reflected in a single daily drug dose, is desirable from the standpoint of compliance (2, 3). In terms of this criterion, conventional salicylates, though widely regarded as first-line antiarthritic drugs, are not highly conducive to patient cooperation. These substances, notably aspirin, must often be taken at frequent intervals during the day, primarily to minimize GI irritation; daily quantities high enough to yield sustained therapeutic blood levels may be expected to cause prohibitive side effects when given as only one or two doses. Paradoxically, however, the inadequate compliance such a complex drug regimen might entail could undermine maintenance of therapeutic blood salicylate levels (4).

Published data indicate the feasibility of reducing the frequency of salicylate doses in arthritis. A recently developed nonacetylated drug of this class, choline magnesium trisalicylate (I) has been successfully used on a twice-daily basis in patients with rheumatoid arthritis or osteoarthritis (5–8). It was of interest to determine whether pharmacokinetic data would support even less frequent administration of this drug. We therefore conducted the present crossover bioavailability study in healthy volunteers to compare once-daily and twice-daily treatment schedules of I.

EXPERIMENTAL SECTION

Protocol—Twenty-four healthy males, 19–34 years old (mean, 28 years), whose weights were within 10% of ideal (58.6–96.1 kg; mean, 74.7 kg), took part in the study, which was conducted in accordance with a protocol approved by an institutional review board. The subjects had given written informed consent and were judged to be in good health on the basis of physical findings and the results of blood chemistry determinations, hematological work-up, routine urinalysis, and tests for fecal occult blood. None had a history of sensitivity to salicylates or of serious GI, hepatic, renal, or hematological

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Table I—Steady-State 24-h Serum Salicylate Levels in a Crossover Comparison of Once- and Twice-Daily Administration of I

Salicylate Dosage	Baseline[b]	Serum Salicylate Values, mg/dL[a] 1	2	4	8	12	18	23.5
1500 mg twice daily	13.5 ± 5.1	16.5 ± 5.7	18.9 ± 5.1	18.1 ± 4.4	14.7 ± 4.4	12.3 ± 4.6	7.0 ± 4.2	3.4 ± 3.5
3000 mg once daily	9.1 ± 4.8	17.8 ± 6.7	22.2 ± 6.4	22.9 ± 4.1	20.6 ± 3.4	17.1 ± 4.5	12.1 ± 4.4	7.0 ± 4.5

[a] Mean ± *SD*; $n = 24$. [b] "Trough" value.

Table II—Selected Steady-State Pharmacokinetic Values in a Crossover Study of Serum Salicylate Levels after Administration of I

Salicylate Regimen (6 d)	Observation Period, h	Pharmacokinetic Values After Last Dose of Regimen[a] AUC, mg·dL/h	C_{max}, mg/dL	t_{max}[b], h	$t_{1/2\ (el)}$, h	k_{el}, h^{-1}
1500 mg, twice daily	12	174.0 ± 47.7	20.0 ± 5.1	2.5 ± 1.1	7.2 ± 3.6	0.11 ± 0.04
3000 mg, once daily	24	367.3 ± 82.8	24.9 ± 4.1	4.2 ± 3.2	8.2 ± 3.5	0.10 ± 0.04

[a] Mean ± *SD*; $n = 24$. [b] Calculated assuming first-order pharmacokinetics.

disorders. The volunteers had been instructed to take no antibiotics for at least 15 d and no other drugs for at least 7 d before the start of the study; no additional medication was allowed during the trial.

Two groups, approximately comparable in terms of the body weights, were formed by random assignment; the trial proceeded in two phases, the second involving reversal of the initial dosage schedules. For phase 1, 12 subjects received four tablets of I[1] (equivalent to 3000 mg of salicylate) daily as two equal fractions, 12 h apart, for 6 consecutive days. The remaining 12 volunteers were given a single daily four-tablet dose in the evening, also for a 6-d period. The subjects reported to the research facility to receive each supervised dose, and all doses were ingested after a 1-h fast, with 180 mL of water. After a 1-week wash-out period, the treatment schedules were reversed (phase 2). Subjects treated on a twice-daily basis in phase 1 now received the single daily dose, and *vice versa*. All other experimental conditions remained unchanged.

Blood samples were obtained for the determination of "trough" serum salicylate levels just before drug administration on the evenings of study days 4–6 and 18–20. Blood specimens were also drawn at 1, 2, 4, 8, 12, 18, and 23.5 h after the final doses, *i.e.*, those doses ingested in the evenings of day 6 and day 20. The subjects were confined to the facility for sampling. The serum salicylate values obtained at these time points were used to elucidate the pharmacokinetics associated with each dosage schedule. The subjects were questioned at least once daily concerning their well-being, and the clinical and laboratory evaluations performed at the start (physical examination, blood chemistry profile, hematological work-up, urinalysis, and test for fecal occult blood) were repeated at its conclusion.

Assay Method—Serum salicylate concentrations were measured by a modification of the HPLC method described by Peng *et al* (9). After the addition of a known amount of phthalic acid as an internal standard, the serum was acidified with 85% phosphoric acid. Salicylate and internal standard were extracted into a 50:50 (by volume) mixture of benzene–ethyl acetate by vigorous mixing. After centrifugation, the organic phase was transferred to a clean tube, made alkaline by the addition of ammonium hydroxide, and evaporated to dryness at room temperature under a stream of nitrogen. The residue was dissolved in a small volume of mobile phase, acetonitrile–0.1 M phosphoric acid (40:60, v/v). An aliquot was injected onto a reverse-phase C_{18} high-pressure liquid chromatographic column. The effluent from the column was monitored continuously at a wavelength of 237 nm. Average retention times were 3.0 min for the internal standard and 7.5 min for salicylic acid when the mobile phase was pumped at a rate of 1.3 mL/min. The assay was linear over the range of salicylate concentrations from 1.5 to 50 mg/dL. As little as 1.5 mg/dL of salicylate could be measured quantitatively; lower concentrations were reported as zero. The day-to-day coefficient of variation of the assay was 10.6% at a concentration of 7.5 mg/dL.

RESULTS

There was no indication that any of the subjects violated the protocol or took drugs other than the assigned tablets. None of the volunteers left the trial before its conclusion.

Blood samples obtained just before drug ingestion on days 4–6 and 18–20 of treatment yielded consistent "trough" levels. These data indicated that the volunteers had reached steady-state concentrations by the time of the dose administered on the evening of the sixth day of each phase of the study, before sampling for the 24-h curves. Mean serum "trough" levels were within the therapeutic range of 5.0–30.0 mg/dL of salicylate.

The mean ± 1 *SD* values for the b.i.d. schedule were 13.4 ± 5.1, 12.4 ± 5.0, and 13.5 ± 5.1 mg/dL for the final 3 d of dosing in sequence. The corresponding values for the once-a-day dosage regime were 8.4 ± 4.9, 8.5 ± 4.6, and 9.1 ± 4.8 mg/dL. The 24-h serum salicylate curves showed sustained anti-inflammatory blood levels with both schedules (Table I; Fig. 1). Seventeen subjects still exhibited substantial concentrations (>10 mg/dL) 18 h after the once-daily 3000-mg dose.

The measured areas under the curves (AUC) at steady state (Table II) were proportional to the dose of I administered; the mean area computed over the 12-h interval after the subjects received 1500 mg of salicylate was about half the mean area calculated over the 24-h period after one 3000-mg dose was ingested at steady state.

The bioavailability of the single dose relative to that of the divided dose was 1.06. This value respresented the ratio of the AUC values (0–24 h/0–12 h) divided by the ratio of the respective doses (3000/1500) and did not differ significantly from the theoretical value of 1.0. Due to the very complex nonlinear pharmacokinetics of salicylate, the ratio of 1.06 can not be used as absolute evidence for equal absorption *via* the two dosage regimens. However, the data do suggest that the relative bioavailability from the two dosage regimens is probably very similar.

Two-way analyses of variance yielded the following significant differences between treatments in comparisons involving 24-h and 12-h observation periods for single 3000-mg and 1500-mg doses of salicylate, respectively: mean values for serum salicylate peak levels (C_{max}) and time to peak (t_{max}) were significantly higher ($p < 0.001$ and $p = 0.02$, respectively) with once-daily administration. No significant differences in elimination half-life ($t_{1/2\ (el)}$) or the elimination rate constant (k_{el}) was noted (Table I).

The incidence of apparently drug-related complaints was similar with both dosage schedules (Table III). They involved a total of eight subjects, three affected during the once-daily regimen only and four during the twice-daily schedule only; one volunteer experienced undesirable symptoms with both regimens (tinnitus with once-daily treatment and "stomach ache" with b.i.d. administration). The side effects were those generally expected to occur with salicylate use. They were usually transient despite continued treatment, in

Table III—Side Effects Associated with Repeated Administration of I

Salicylate Dosage Schedule[a]	Period	Subject	Side Effects
A	1	13	tinnitus
	1	18	tinnitus
	1	20	tinnitus
	2	22	tinnitus
	2	22	"stomach ache"
B	1	2	tinnitus
	1	6	"stomach pain"
	1	7	"upset stomach"
	2	18	"stomach ache"
	1	19	tinnitus

[a] A 7-d wash-out period intervened between dosage schedules. Schedule A is 3000 mg once daily for 6 d; Schedule B is 1500 mg twice daily for 6 d.

[1] Trilisate 750 tablets, lot no. P-55; The Purdue Frederick Co., Norwalk, Conn.

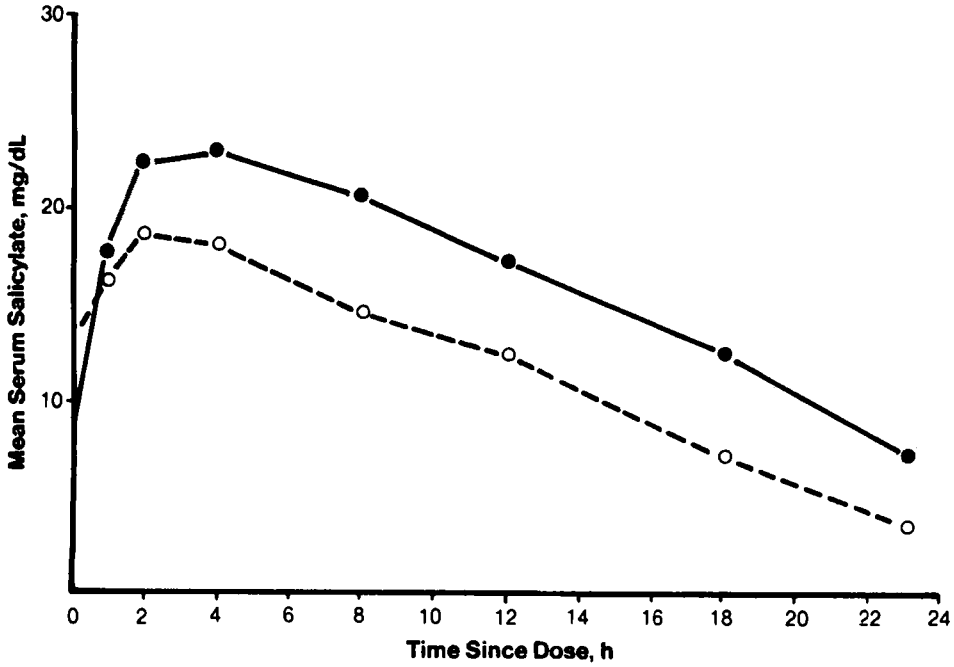

Figure 1—*Steady-state serum salicylate levels in 24 healthy subjects after final doses of two 6-d regimens of I administration. Key: (●) at the end of once-daily treatment with 3000 mg of salicylate; (○) at the end of twice-daily treatment with 1500 mg of salicylate.*

most cases occurred on a single day only, and did not require any of the subjects to leave the study. The complaints were more frequently voiced during the first phase of the study than during the second, regardless of treatment schedule.

DISCUSSION

Our results indicate the equal bioavailability of single daily and b.i.d. doses of I under the conditions of this trial and support the feasibility of once-daily treatment with this drug. They further show that daily ingestion of four-tablet doses yields mean "trough" and peak serum salicylate levels within the therapeutic range. However, since the pharmacokinetics of salicylate vary substantially from individual to individual, the choice of antiarthritic regimen should probably be individualized on the basis of blood concentrations and clinical response.

Once-daily use by arthritic patients is not known to be feasible with other salicylates now available, and hence, within this class of drugs, appears to be limited to choline magnesium trisalicylate (I). Obviously, drug safety is a major consideration in this respect. In the present study, physical examination and laboratory investigations, as well as analysis of reported side effects, indicated comparable safety of both dosage schedules of I in the healthy young males studied. While tinnitus appeared to be the predominating side effect during the once-daily regimen and GI symptoms occurred mainly with b.i.d. administration, the numbers of subjects involved were too small to indicate any trends in this regard.

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