J Int Med Res (1979) **7**, 90

Salicylsalicylic Acid Revisited: A Multicentre Study

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Twenty-eight medical specialists (internists, rheumatologists) selected 102 primarily arthritic patients for a two-week efficacy and safety field study of salicylsalicylic acid. Data were gathered on pain, morning stiffness, range of motion, serum salicylate concentration, erythrocyte sedimentation rate (ESR) and gastro-intestinal bleeding before and after a 15-day drug trial. Results showed a 67% favourable clinical response in the physician's global evaluation and a 60% improvement in pain; the drug itself was well tolerated by 96% of patients. Response correlations with morning stiffness and range of motion were equivocal. Of fifty-four patients examined before and after treatment for intestinal bleeding, only two (3·7%) had detectable faecal blood loss. Good clinical response had a statistically significant association with serum drug concentrations of 13·6 to 13·8 mg%; unsatisfactory response was noted in those patients with mean serum salicylate levels of 8·6 mg%. ESR decreased or was unchanged in thirty-five patients with satisfactory clinical response and in fourteen patients with unsatisfactory response.

Introduction

Re-evaluation of salicylsalicylic acid* (salsalate) gradually defines it as a viable alternative to regular aspirin therapy, chiefly in terms of equivalent clinical efficacy and improved safety considerations. Recent studies (Liyanage & Tambar 1978, Rubin 1964, Paris & Newfield 1963) have clearly demonstrated that salsalate and aspirin are therapeutically indistinguishable.

Salsalate's insolubility in acidic media minimizes gastric erosion and bleeding to placebo levels (Leonards 1969, Edmar 1971, Thune 1968). A controlled study using the Cr^{51} methodology has confirmed this (Cohen 1979). The drug is rapidly absorbed and, like aspirin, metabolized by esterases to salicylic acid (SA); the plasma half-life of the latter, whether derived from salsalate or aspirin, is similar (Nordqvist, Harthon & Karlsson 1965, Levy 1965). Salsalate, an ester of two SA molecules, yields 28% more active metabolite than aspirin when equal amounts of the drugs are used. Thus lower dosages of salsalate are equipotent with aspirin and thereby minimize side-effect liability. This is particularly important in long-term therapy of chronic diseases.

As part of an extensive programme of clinical investigation, the following field study clarifies some matters of efficacy and safety concerning the use of salsalate. Data on arthritic patients were gathered from twenty-

*Disalcid®, Riker Laboratories Inc., Northridge, CA 91324, U.S.A.

0300-0605/79/010090-06 $02·00

eight rheumatologists or internists in widely dispersed private practices around the United States.

Materials and Methods

This open field study used no placebo groups and was designed to determine the efficacy and safety of salsalate. One hundred and two patients, primarily with rheumatoid and osteoarthritis, were selected for participation. They were interviewed and examined by twenty-eight medical specialists in private practice. Following baseline evaluations, patients were directed to take 3 g (2 × 500 mg t.i.d.) of salsalate daily and then report back for further evaluation in 15 days. Individual dosage adjustments could be made as required; all other known salicylate sources were interdicted prior to and during the study period.

Response variables selected for observation were pain intensity, morning stiffness, range of motion (ROM), physician's global assessment, and side-effects. Laboratory analyses in most patients included serum salicylate concentrations (mg%), erythrocyte sedimentation rate (ESR), and examination of stool specimens for evidence of gastrointestinal bleeding. These data were analyzed by the following statistical techniques; binomial test, Chi-square, and contingency coefficient.

Results

Patients in three diagnostic categories completed this study: forty-one with rheumatoid arthritis (RA), fifty with osteoarthritis (OA), and eight described as 'other' (no diagnosis in five, one with calcaneal spur, one with inflammation of left knee, and one

Table 1

Changes in pain, morning stiffness, and range of motion after 15 days of treatment

Diagnoses	*Degree of change*	*Patients* showing changes in:*		
		Pain	*Morning stiffness*	*Range of motion*
RA (n = 41)	Relief	24	22	20
	Unchanged	13	16	18
	Worse	1	0	0
OA (n = 50)	Relief	29	20	12
	Unchanged	19	27	33
	Worse	2	2	0
Other**	Relief	4	3	5
	Unchanged	3	4	2
	Worse	0	0	0
Overall	Relief	57	45	37
	Unchanged	35	47	53
	Worse	3	2	0

*Data not available for all patients

**No diagnosis given for Patients Nos. 4, 49, 72, 90, 100;
No. 54 had calcaneal spur;
No. 60 had inflammation of left knee;
No. 73 had SLE

with SLE). Mean age for all patients was 55·1 years, ranging from 22 to 84 years. OA patients, as expected, were oldest, with a mean age of 60·4 years. Mean weight was 162·3 pounds (range 80–250). There were seventy-four women and twenty-eight men. Of the ninety-eight patients for whom initial pain data were obtained, only ten had mild pain. The remaining eighty-eight patients had moderate to severe pain.

Response variables of pain, morning stiffness, and ROM were based on subjective estimates by patients. Of these, only pain had numerical superiority in all disease groups in terms of relief during salsalate treatment (Table 1): fifty-seven patients (60%) reported relief, thirty-five remained unchanged and three were worse. No change score was statistically significant, however. In over half the patients morning stiffness was unchanged or worse; only in the RA group was this variable appreciably relieved. ROM results were not encouraging. But here again, the RA group had slightly more patients relieved than unchanged.

Serum salicylate concentrations varied widely from patient to patient, in one to as high as 45 mg% during treatment. However, in the sixty-seven patients for whom such values were calculated, salicylate concentrations were as expected for ordinary out-patient use (Brewer 1966) (Table 2). It is particularly interesting to look at the association between drug concentrations and global estimates of clinical efficacy made by the physician. Unsatisfactory response was associated with a group mean drug concentration of 8·6 mg% in twenty-three patients, while satisfactory to excellent response was significantly associated in forty-four patients (66%) with concentrations of 13·6 to 13·8 mg% ($p<0·05$). These findings support the concept of a minimum effective serum salicylate concentration. Similar grouping with ESR data (Table 3) fails to show any clear-cut association of change with clinical response to treatment, as previously noted by Deodhar *et al* (1977). A satisfactory response is associated with a decrease or no change in ESR in thirty-five patients, while only fourteen patients with no change or decrease fell into the unsatisfactory category.

Faecal blood loss findings were less equivocal. Before-and-after examinations were successfully carried out on fifty-four patients. Only two of these (3·7%) had detectable increases (Figure 1). One patient had a trace at both observations.

Overall assessment of treatment efficacy made by the individual physicians found thirty-six with unsatisfactory and sixty-three with satisfactory or excellent response. Adequate response was seen in 63% of RA

Table 2

Association of mean serum salicylate levels and physician's global estimate of clinical efficacy

Response variable	*Number of patients*	*Mean serum salicylate level (mg%)*
Excellent	12	13·8
Satisfactory	32	13·6
Unsatisfactory	23	8·6

Table 3

Association of erythrocyte sedimentation rate (ESR) and physician's global estimate of clinical efficacy

Response variable	*(ESR)*		
	Decreased	*Increased*	*Unchanged*
Satisfactory	28	15	7
Unsatisfactory	10	14	4

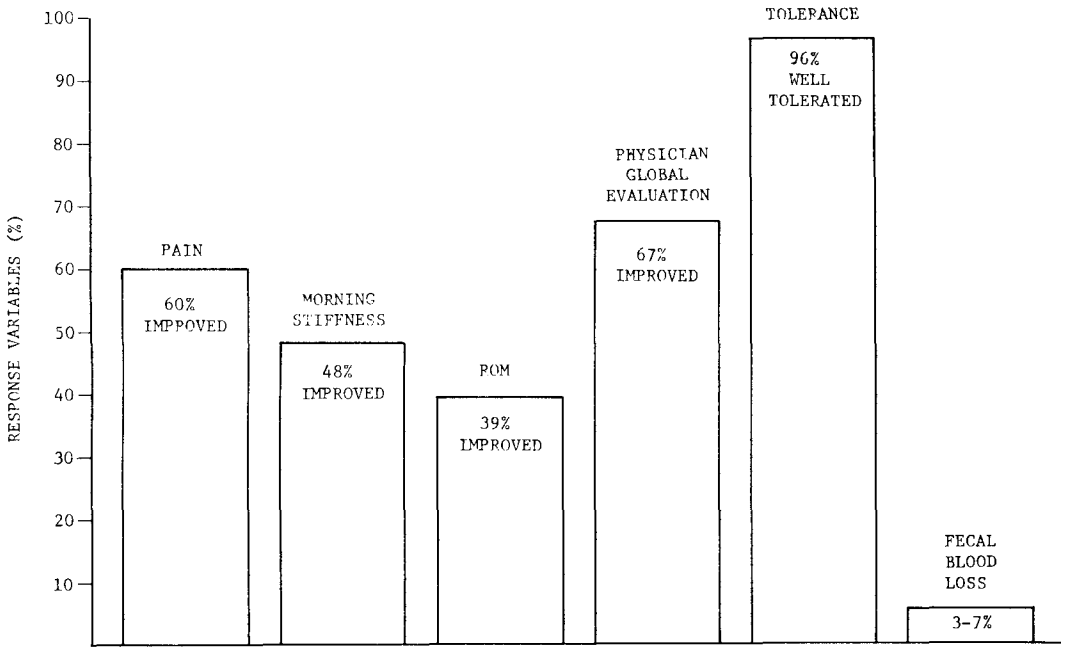

Fig 1 *Overall results from multiclinic salsalate field study*

patients, 62% of OA patients, and 75% of 'other' patients (Table 4). Overall, the physicians' global assessment was adequate in 67% of patients (Figure 1).

Treatment side-effects were those commonly seen in patients taking repetitive daily doses of salicylates (Table 5). Frank intoxication occurred in one individual who continued to take additional salicylate during the 15-day trial. He was removed from the study. Three other patients were discontinued due to lack of tolerance to salsalate. The only other observation of interest involved five reports of hearing loss from one investigator. On the chance that this might have resulted from toxic serum salicylate levels, each individual's report was analyzed. Serum concentrations ranged from 7 to 19 mg% and the group mean was 10·82 mg%. This is well below established toxic concentrations of salicylate. To the best of our knowledge, these hearing decrements were not permanent.

Table 4

Global assessment of treatment efficacy (%)

	Clinical result (%)		
Diagnoses	*Excellent*	*Satisfactory*	*Unsatisfactory*
RA	21·9	41·5	36·6
OA	14·0	48·0	38·0
Other*	25·0	50·0	25·0

See footnote Table 1

Table 5

Side-Effects: Treatment group, side-effect, and clinical results

Pt. No.	*RA*	*Result**	*Pt. No.*	*OA*	*Result*
2	Salicylate intoxication**	U	5	Indigestion, lightheaded	S
8	Pruritis on neck	U	9	Pounding sensation in head	U
16	Severe abdominal discomfort, nausea, diarrhoea	U	10	Constipation	S
			24	Nausea (discontinued Rx)	U
29	Loss of hearing	X	40	Dizzy, tinnitus (decreased Rx)	U
30	Loss of hearing	S	41	Dizzy, tinnitus	U
32	Loss of hearing	U	42	Dizzy, stomach cramps	U
33	Loss of hearing	X	46	Slight epigastric distress	S
39	Loss of hearing	S	48	Nausea (cleared)	X
63	Severe lightheaded, Mental confusion, (discontinued 4th day)	U	61	Heartburn (discontinued Rx)	U
			67	Lightheaded, voice change	U
76	Dizziness, tinnitus	U	80	MM cramps (discontinued Rx)	U
87†	Severe tinnitus	X	87	Severe tinnitus (decreased Rx)	X

* U = Unsatisfactory, S = Satisfactory, X = Excellent
** Patient continued to take salicylate-containing medication in addition to test drug
† Patient No. 87 was diagnosed as both RA and OA by investigator

Discussion

This study demonstrates the potential for salsalate as an alternative to regular aspirin therapy. Results were in accordance with a similar multicentre evaluation of this drug in Great Britain (Marshall & Lewis 1978), except that better improvements in morning stiffness and ROM were noted there. Our investigation reveals somewhat better 'global' improvement (67% vs 63%). Only 8% of the patients reported gastro-intestinal side-effects. Patient tolerance of the drug was 96%. Additionally, we were encouraged to note an incidence of gastro-intestinal bleeding of only 3·7%, corroborating earlier blood-loss studies by Cohen (1979), Leonard (1969), and others (Edmar 1971, Thune 1968), in which salsalate was shown to have negligible erosive effects on intestinal mucosae.

Serum salicylate concentrations in a sixty-seven-patient subgroup were found to associate well with global estimates of clinical efficacy made by the physician. Satisfactory to excellent response was significantly associated with blood levels of 13·6 to 13·8 mg%, whereas those patients with an unsatisfactory rating had a mean level of 8·6 mg%. Paulus *et al* (1971) state that serum concentrations of salicylate of 15 mg% or more are therapeutically useful. However, French and Mildon (1978) note in a recent report on overnight maintenance of serum salicylate levels that 10 to 30 mg% is a widely accepted therapeutic range.

In a two-week out-patient study similar to ours, Liyanage and Tambar found near identical mean drug levels (13·5 mg%) associated with adequate clinical response

(Liyanage & Tambar 1978). Another two-week study using twenty healthy volunteers housed in a research facility, with all dosage administration closely watched, fourd mean drug levels of 12·0 mg%. Highest levels occurred on the fifth day of administration (15·98 mg%). All determinations were made 12 hours after the last dose of salsalate (Cohen 1979). Other investigators have commented on the wide variability in blood levels even in hospitalized patients taking the same dosages of salicylates, so we feel gratified in attaining effective concentrations in most patients in this out-patient situation.

Acknowledgements

We thank the numerous practitioners who took part in this trial. A detailed list is available on request from the author. Thanks are also due to Ronald J Landry for writing this paper and to Christopher Johnson, PhD for statistical consultations.

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