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Original Article

Tolmetin and salicylate therapy in acute rheumatic fever: Comparison of clinical efficacy and side-effects

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Abstract

Background: The arthritis of rheumatic fever is very responsive to treatment with salicylates, but there are many adverse reactions, especially hepatotoxicity, due to aspirin (acetylsalicylic acid) therapy. These side-effects change the course and duration of rheumatic fever. Other non-steroidal anti-inflammatory drugs may be equally effective, although no reports are available.

Methods: We studied 72 patients with rheumatic fever who were admitted to Dr Sami Ulus Children's Hospital between 1995 and 1999. Twenty patients with arthritis were treated with tolmetin (25 mg/kg per day; group I) and 52 patients with arthritis and/or mild carditis were put on aspirin therapy (75–100 mg/kg per day) for 4–6 weeks (group II). Arthritis had disappeared at the same time in both the aspirin and tolmetin groups ($P = 0.675$).

Results: The erythrocyte sedimentation rates of patients upon admission, at the first week and at the end of therapy were not different in the two groups ($P > 0.05$). No adverse effect of tolmetin therapy was observed, whereas side-effects of salicylate were observed in 19 patients (36.5%) in the aspirin group. Hepatotoxicity, gastric irritation and salicylism were found in 16, four and three patients, respectively. Renal toxicity and Reye syndrome were not demonstrated. Because of these side-effects of aspirin, therapy had to be stopped for 10–20 days and the duration of hospitalization in this group was lengthened unnecessarily.

Conclusion: Tolmetin was safe and effective treatment for arthritic rheumatic fever patients without carditis. Tolmetin can be used particularly in patients who cannot tolerate aspirin.

Key words aspirin, rheumatic fever, tolmetin.

Rheumatic fever is a multisystem inflammatory disease that occurs as a delayed sequel to group A streptococcal pharyngitis.[1] Although the incidence of acute rheumatic fever (ARF) and its sequel, chronic rheumatic heart disease, has declined in developed countries, it remains the most common cause of acquired heart disease in children and young adults worldwide.[2,3]

Eradication of the streptococcus is the first step of therapy for ARF. All patients with ARF should be placed on bed rest and monitored for carditis. Anti-inflammatory agents, namely salicylates and corticosteroids, remain the first-line agents in the treatment of rheumatic fever and usually provide dramatic clinical improvement.

Generally, salicylates alone are used for arthritis and carditis without cardiomegaly, steroids being added if salicylate therapy is inadequate or there is severe carditis.[1]

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The arthritis of ARF is typically very responsive to salicylates; however, the occurence of adverse reactions is inevitable. Adverse effects of aspirin therapy in children are mainly gastric irritation, tinnitus and/or diminished hearing and hepatotoxicity. These side-effects change the course and duration of therapy.

For patients who cannot tolerate aspirin, other non-steroidal anti-inflammatory drugs can be used.[4] Other non-steroidal anti-inflammatory drugs might be equally effective, although little documentation of their efficacy in rheumatic fever is available.

The aim of the present study was to determine the clinical efficacy of tolmetin therapy and to compare the side-effects of tolmetin and aspirin in ARF.

Methods

We prospectively studied 72 patients with ARF who were admitted to Dr Sami Ulus Children's Hospital between 1995 and 1999.

All patients were examined by a pediatric cardiologist when admitted to hospital and the diagnosis of ARF was

Table 1 Age distribution of patients with acute rheumatic fever

Age (years)	Group I	Group II
0–4	0 (0)	0 (0)
5–8	6 (30)	12 (23)
9–12	11 (55)	26 (50)
13–15	3 (15)	14 (27)
Total	20 (100)	52 (100)

Data show the number of patients, with percentages given in parentheses.

The median age for patients given tolmetin and aspirin (groups I and II, respectively) was 10 years.

based on the modified Jones criteria.[1] Patients were examined weekly for complete blood count, erythroctye sedimentation rate, C-reactive protein (CRP), liver and renal function tests, protein, albumin, prothrombin and partial thromboplastin time and urinalysis. Throat cultures, anti-streptolysin-O (ASO) titers, telecardiograms and electrocardiograms of all patients were also obtained. M-mode, two dimensional and Doppler echocardiographic examinations were performed by a pediatric cardiologist using a Hewlett-Packard 1000 ultrasound system (Hewlett-Packard, Palo Alto, CA, USA) equipped with 3.5 and 5.5 MHz transducers in order to document the existence of valvular insufficiency and pericardial effusion.

Twenty patients with arthritis were treated with tolmetin (25 mg/kg per day, divided into three daily doses with food; group I). Tolmetin therapy lasted 4 weeks.

Fifty-two patients with arthritis and/or carditis were put on salicylate therapy (group II). Salicylates were administered to patients with arthritis at a dose of 75 mg/kg per day for 4 weeks and at 100 mg/kg per day, divided into four daily doses with food, for 6 weeks to patients with mild carditis.

All patients were hospitalized. Patients who had moderate to significant carditis and cardiac failure were excluded from the present study. Adverse effects of tolmetin and salyclate therapy were monitored. Arthritis resolution was defined as the disappearance of heat, pain and swelling of the affected joint. Patients with arthritis and carditis were discharged at the end of 4 and 6 weeks, respectively, although hospitalization was expanded to 8 weeks in cases of toxicity.

Patients were discharged with the recommendation that they use benzathine penicillin G for the prophylaxis of streptococcus (1.2 million units for patients weighing 27 kg or more and 600 000 units for those weighing less than 27 kg) every 21 days.

The Mann–Whitney *U*-test and χ^2 test were used for statistical investigations.

Results

Seventy-two patients with ARF were diagnosed, treated and followed up in our hospital from 1995 to 1999. The study group consisted of 36 girls (50%) and 36 boys (50%). The female : male ratio in groups I and II was 0.82 and 1.08, respectively. The age distribution of the children is given in Table 1. The median age was 10 years for both groups. The majority of patients were between 9 and 12 years of age (50.1%). Most patients in both groups were from rural areas and had a poor socioeconomic status.

Table 2 Major and minor manifestations of patients with acute renal failure

Manifestation	Group I (n = 20)	Group II (n = 52)	P
Arthritis alone	20 (100)	17 (32.7)	
Carditis alone*	–	25 (48.1)	
Arthritis and carditis*	–	10 (19.2)	
Arthralgia	20 (100)	43 (82.7)	<0.05
Fever	13 (65)	31 (59.6)	NS
Elevated acute phase reactants			
ESR	20 (100)	48 (92.3)	NS
CRP	20 (100)	44 (84.6)	NS
Positive throat culture	–	2 (3.8)	NS
Prolonged PR interval	6 (30)	9 (17.3)	NS
Elevated streptococcal Ab titer	15 (75)	51 (98.1)	<0.05
Previous ARF attack	5 (25)	16 (30.8)	NS

Data show the number of patients, with percentages given in parentheses.

*Mild carditis. Group I, patients given tolmetin; group II, patients given aspirin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Ab, antibody; ARF, acute rheumatic fever; NS, not significant.

The distribution of the major and minor manifestations of group I and II patients is given in Table 2.

There were no statistically significant differences between the two groups with regard ro CRP concentrations on admission and duration of arthritis. On admission, CRP in groups I and II was 29.2–70.8 mg/L (median 42.6 mg/L) and 31.5–75.2 mg/L (median 48.4 mg/L), respectively.

The history on admission in groups I and II was 9–15 days (median 12 days) and 10–15 days (median:13 days), respectively.

Of 20 patients in group I, four had had a second relapse, whereas of the 52 patients in group II, 17 had had a second relapse.

We evaluated and also compared the time of resolution of the arthritis after initiation of therapy in groups I and II (Table 3). Arthritis was resolved with in 2–6 days in groups I (mean 3.65 ± 1.35 days) and II (mean 3.81 ± 1.30 days). No statistically significant difference was found between the two groups ($P = 0.675$).

Erythrocyte sedimentation rates of patients on admission, at the first week and at the end of therapy are given in Table 4. There was no statistically significant difference between the two groups ($P > 0.05$).

Table 3 Time required for resolution of arthritis after initation of therapy in patients given tolmetin and aspirin (groups I and II, respectively)

Days	Group I (n = 20)	Group II (n = 27)
2	4 (20)	4 (14.8)
3	7 (35)	9 (33.3)
4	4 (20)	6 (22.2)
5	2 (10)	4 (14.8)
6	3 (15)	4 (14.8)
Total	20 (100)	27 (100)

Data show the number of patients, with percentages given in parentheses. P = 0.675.

Table 4 Erythrocyte sedimentation rates (ESR) in patients given tolmetin and aspirin (groups I and II, respectively)

ESR (mm/h)	Group I (n = 20)	Group II (n = 52)	P
On admission	91 ± 23 (90)	82 ± 18 (76)	NS
First week	54 ± 22 (60)	53 ± 14 (50)	NS
At the end of therapy	21 ± 9 (20)	18 ± 5 (18)	NS

Data are the mean ± SE, with median values given in parentheses. NS, not significant.

The side-effects of tolmetin and salicylates were evaluated (Table 5). No adverse effect of tolmetin therapy was observed. Side-effects were detected in 19 patients (34.6%) in the salicylate group. Hepatotoxicity, gastric irritation and salicylism were observed in 16, four and three patients, respectively.

Hepatotoxicity was noted in the first week in the salicylate group. Elevations of aspartate transaminase (AST) and alanine transaminase (ALT) were 100–300 U/L in four patients and 300–1000 U/L in 12 patients. Alkaline phosphatase and the prothrombin time of these patients were normal. The serum salicylate concentrations of the 16 patients ranged from 14 to 42 mg/dL (> 30 mg/dL in eight patients). No evidence of jaundice and chronic hepatotoxicity was recorded.

Of the 16 patients, four also had gastric irritation. Liver function studies returned to normal values in these patients 5–20 days after withdrawal of aspirin therapy. Because of these side-effects, the course of therapy was prolonged by between 5 and 20 days.

Salicylism occurred in three patients in the first week. Drowsiness, irritability and hyperpnea were detected in these patients. Serum salicylate levels in these patients were 65, 56 and 46.7 mg/dL. Salicylate therapy was discontinued, their stomach contents were emptied, intravenous fluid was given and alkaline diuresis was induced. No peritoneal dialysis or hemodialysis were used. The liver function tests of these patients were normal.

None of our patients developed carditis after starting tolmetin or salicylate.

Table 5 Side-effects of tolmetin (group I) and salicylate (group II) therapy

Side-effect	Group I (n = 20)	Group II* (n = 52)	P
Gastric irritation	0 (0)	4 (7.7)	NS
Hepatotoxicity	0 (0)	16 (30.8)	<0.05
Salicylism	0 (0)	3 (5.8)	NS
Any side-effects	0 (0)	19 (36.5)	<0.05

Data show the number of patients, with percentages given in parentheses. *Four patients who had gastric irritation also had hepatotoxicity. NS, not significant.

Reye syndrome, renal toxicity, coagulation abnormalities and hearing defects were not detected.

Discussion

There is no specific treatment for ARF. The duration and nature of therapy are mainly dependent upon the presence and severity of carditis during the initial attack.

The treatment modalities for ARF are bed rest, penicillin for streptococcus and anti-inflammatory drugs.[1–5] Salicylates are one of the non-steroidal anti-inflammatory drugs remaining as first-line agents in treatment of arthritis and mild carditis and usually bring about a dramatic clinical improvement. Salicylates exert their anti-inflammatory, analgesic and antipyretic effects in part by irreversibly acetylating and inactivating cyclo-oxygenase, thus inhibiting the biosynthesis and release of prostaglandins.[6,7] In practise, salicylate is an acceptably safe drug if it is administered and monitored carefully. Because of the widespread use of salicylates and their substantial pharmacological activity, the occurence of adverse reactions is inevitable. Both adverse and beneficial effects tend to be dose related, necessitating careful evaluation of the benefits-to-risks ratios. Gastric irritation, tinnitus and/or diminished hearing and hepatotoxicity are important toxicities. Reye syndrome, hypersensitivity, salicylism and renal and hematologic abnormalities are rarely seen. Although gastric irritation is the most common toxic effect (50%) of salicylates, peptic ulceration and overt gastrointestinal bleeding are rare in children taking aspirin.[6,7] Salicylate-induced hepatotoxicity has been observed in several studies. Hamdan *et al.* found that hepatotoxicity occurred in 17% of patients with ARF.[8] In another study, this rate was found to be 24%.[9] Arthreya *et al.*[10] noted abnormalities of liver function in 22 of 34 salicylate-treated children with juvenile rheumatoid arthritis, but in none of eight treated control children. Similar findings were reported by Miller and Weissman[11] and Bernstein *et al.*,[12] who also noted that hepatotoxicity was often associated with active arthritis. Because of these

abnormalities, the duration of treatment and the course of the disease were influenced.

The arthritis of ARF is typically very responsive to salicylates. For patients who cannot tolerate aspirin, other non-steroidal anti-inflammatory drugs can be used. The use of non-steroidal anti-inflammatory drugs other than aspirin for the treatment of ARF has been reported by Dzhuzenova *et al.*[13] and Uziel *et al.*[14] Dzhuzenova *et al*. used indomethacin in 102 patients with ARF, whereas Uziel *et al.* used naproxen in 19 patients with ARF. Both groups observed favorable results in all patients. There are no data available regarding tolmetin therapy in the arthritis of ARF. For this reason, we wanted to observe and compare the efficacy and adverse reactions of tolmetin and aspirin in such patients.

Tolmetin is the only pyrole derivative used in clinical practice. It is a potent analgesic, antipyretic and anti-inflammatory agent, exerting its anti-inflammatory effect by inhibition of cyclo-oxygenase. The pediatric dose is approximately 25 mg/kg per day (range 15–30 mg/kg per day).[8,9] Tolmetin seldom produces marked elevations of the transaminase enzymes observed with aspirin. In one study consisting of patients with juvenile rheumatoid arthritis, elevated AST values occured in one of 53 (1.9%) children treated with tolmetin and in 13 of 54 children (24.1%) on aspirin alone.[15] Nephrotic syndrome and hemolysis are rarely associated with the use of tolmetin.[16–18] Gastric irritation occurs less with tolmetin than with salicylate. The results of long-term studies of adult patients with rheumatoid arthritis demonstrated that tolmetin is an effective anti-inflammotory agent with an acceptable record of safety.[19–21] In the present study, we demonstrated that the clinical efficacy of tolmetin and aspirin is the same. No adverse effects were observed following the use of tolmetin. Hepatotoxicity due to salicylate was detected more frequently; however, gastric irritation was observed less than in previous reports. The possible reason for less gastric irritation in the present study is our careful attention about giving doses immediately after meals. Hepatic enzymes of patients in the present study who showed hepatotoxicity due to salicylate returned to normal levels within 5–20 days after discontinuation of the drug only. This finding is comparable with reports about the reversibility of salicylate hepatotoxicity.

The serum salicylate levels of our three patients with salicylism were rather high. In any case, because the patients were hospitalized, interventions were made immediately symptoms became apparent and no fatalities occurred. We have not detected any other side-effect due to aspirin.

In conclusion, an interruption in the therapeutic schedules of patients on aspirin and an extension in hospitalization due to the side-effects of aspirin were observed. In contrast, no side-effects were detected in patients taking tolmetin.

We believe that tolmetin can be used, particularly in patients with arthritis. In cases with carditis, there is need for further investigations.

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