Choline magnesium trisalicylate in patients with aspirin-induced asthma

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ABSTRACT: Treatment of inflammatory diseases of asthmatics can be a serious problem since some patients show intolerance to aspirin and other non-steroidal, anti-inflammatory drugs that are cyclooxygenase inhibitors. Salicylates were believed to be well tolerated, but recent reports have demonstrated that diflunisal and salicylsalicylic acid can precipitate asthma attacks in aspirin-intolerant patients. This study was designed to determine the tolerance of choline magnesium trisalicylate (CMT), a nonacetylated salicylate with potent analgesic and anti-inflammatory activity, in 23 asthmatics with aspirin hypersensitivity confirmed by oral challenge. The study consisted of three phases: 1) patients received increasing doses (50–1,500 mg) of CMT under a single-blind protocol; 2) patients received either a placebo or CMT challenge in a double-blind, randomized, cross-over design; 3) patients received CMT at daily 3,000 mg doses for 1 week. Throughout the study, pulmonary function tests, peak nasal inspiratory flow, and serum salicylate and thromboxane B_2 (TXB_2) levels were monitored. Results showed no airway obstruction, nasal congestion or rhinorrhea after CMT. There was no significant decrease in serum TXB_2 levels, indicating the absence of cyclooxygenase inhibition with CMT. We conclude that choline magnesium trisalicylate is a safe drug for treatment of different anti-inflammatory disorders in asthmatics with aspirin hypersensitivity.
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In about 10% of adult patients with asthma, aspirin and several other non-steroidal, anti-inflammatory drugs (NSAID) precipitate asthmatic attacks and/or rhinorrhea with nasal congestion [1–3]. This is a distinct clinical syndrome called aspirin-induced asthma (AIA). Aspirin intolerance creates many clinical problems, as NSAID are efficacious analgesics, anti-inflammatory and antipyretic agents with increasing therapeutic use. For several years there has been an intensive search for such NSAID which could be used safely in patients with AIA. Among these are salicylamide, benzydamine and dextropropoxyphene. Paracetamol is usually well tolerated, though it might produce sporadically adverse reactions [3–5]. Unfortunately, these are all only moderate analgesics and rather weak anti-inflammatory drugs.

In 1968, SAMTER and BEERS [1], in the classical paper on clinical course of aspirin-induced asthma, concluded that "intolerance to acetylsalicylic acid is certainly not an intolerance to salicylates". This notion was subsequently adopted by most clinicians, though some recent reports questioned its validity [6]. We, therefore, decided to perform a double-blind study to determine the tolerance and safety of choline magnesium trisalicylate (CMT) in aspirin-induced asthma.

CMT is a new salicylate, introduced to the market in 1978 for the treatment of rheumatoid arthritis [7, 8]. Its anti-inflammatory and analgesic effectiveness are similar to that of aspirin and other NSAID. CMT has a long duration of action, good gastrointestinal tolerability, is devoid of anticyclooxygenase activity and does not interfere with platelet function.

Patients and methods

Patients

Twenty three asthmatic patients (14 women and 9 men, age range 26–61 yrs) were studied. They were in stable clinical condition. Fourteen were on oral or inhaled corticosteroids, the dosage of which remained unaltered during the study. One patient was on β-agonist which was stopped 12 h before the trial. Eleven subjects took aminophylline or theophylline regularly, which was withheld 15 h before the study. Cromolyn sodium and ketotifen were discontinued at least one week before the trial. After being briefed on the study procedure and possible side-effects, each patient signed a consent to

Table 1. – Pulmonary function tests determined every 30 min following administration of 750 mg CMT or placebo (double-blind, randomized, cross-over design)

	Baseline values	30 min	60 min	90 min	120 min	150 min	180 min	210 min	240 min
Trilisate									
FVC	3.56 (2.25–6.96)	3.30 (2.08–6.94)	3.26 (2.54–7.23)	3.29 (2.17–7.21)	3.45 (2.27–7.09)	3.35 (2.09–7.14)	3.39 (2.26–7.05)	3.35 (2.16–6.85)	3.52 (2.33–7.08)
FEV_1	2.41 (1.61–4.82)	2.56 (1.34–4.80)	2.48 (1.66–5.06)	2.51 (1.44–5.17)	2.48 (1.52–4.87)	2.43 (1.37–4.65)	2.39 (1.41–4.55)	2.51 (1.47–4.62)	2.53 (1.49–4.80)
MEF_{50}	2.4 (1.3–8.7)	2.7 (1.2–8.5)	2.8 (1.4–8.6)	2.3 (1.3–8.2)	2.6 (1.3–8.5)	2.8 (1.2–8.6)	2.5 (1.2–8.2)	2.5 (1.2–8.1)	2.5 (1.1–8.3)
PNIF*	150 (60–270)	157 (80–260)	150 (60–300)	150 (70–300)	155 (60–290)	150 (70–260)	150 (60–280)	150 (60–270)	160 (70–280)
Placebo									
FVC	3.39 (2.56–6.79)	3.44 (2.68–6.99)	3.26 (2.69–6.73)	3.28 (2.50–6.52)	3.38 (2.56–7.11)	3.35 (2.59–6.54)	3.41 (2.60–7.04)	3.32 (2.63–6.79)	3.37 (2.60–6.81)
FEV_1	2.44 (1.75–4.52)	2.27 (1.77–4.69)	2.36 (1.80–4.39)	2.43 (1.85–4.32)	2.41 (1.65–4.70)	2.43 (1.70–4.50)	2.48 (1.83–4.52)	2.43 (1.64–4.19)	2.34 (1.63–4.43)
MEF_{50}	2.6 (1.4–8.2)	2.4 (1.3–8.5)	2.2 (1.5–8.3)	2.4 (1.4–8.6)	2.5 (1.1–8.3)	2.4 (1.5–8.7)	2.4 (1.4–8.7)	2.4 (1.3–8.7)	2.5 (1.3–8.1)
PNIF*	170 (70–260)	165 (70–250)	155 (60–250)	150 (70–240)	155 (80–240)	155 (70–250)	140 (80–240)	145 (80–270)	135 (80–240)

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; MEF_{50}: mid-expiratory flow at 50% vital capacity; PNIF: peak nasal inspiratory flow; CMT: choline magnesium trisalicylate. Results are presented as median and range in parentheses. PNIF*: values analysed for 12 patients only. No statistically significant differences between pulmonary function parameters following administration of CMT and placebo (Wilcoxon's test).

confirm willingness to participate in the study. In all of the patients the hypersensitivity to aspirin was confirmed by oral challenge tests [3, 9]. Ingestion of threshold aspirin doses produced: 1) at least 20% fall in forced expiratory volume in one second (FEV_1) with clinical symptoms of bronchial obstruction; and/or 2) at least 50% fall in peak nasal inspiratory flow with concomitant rhinorrhea or nasal blockade.

Study design

The study consisted of three parts:
1. Single-blind open study to estimate the rough tolerance of choline magnesium trisalicylate (Trilisate, The Purdue Frederick Co., Conn., USA). The drug was administered to 18 patients in the following way: 1 day 50 mg and 100 mg; 2 day 250 mg and 500 mg; 3 day 1,500 mg. The second dose was given in 2 h intervals on each study day, if the preceding dose did not provoke any adverse reaction. Close medical supervision was provided throughout the test. Pulmonary function tests (see below) were monitored shortly before the drug administration and then every 30 min over the next 5 h.
2. Double-blind, randomized, cross-over study on the effect of CMT *versus* placebo. Fifteen patients received either placebo or 750 mg CMT. Clinical observation, pulmonary function tests and serum levels of salicylate and thromboxane B_2 (TXB_2) (see below) were monitored for 4 h following the challenge. These two challenges were separated by a minimum period of one week.
3. Long-term tolerance of CMT. Seven patients received CMT at a daily dose of 3,000 mg (1,500 mg *b.i.d.*) for seven days. Clinical examination, measurement of pulmonary function tests and serum salicylate level were carried out before and at the end of drug administration (blood for salicylate level was collected 2 h following the last dose of the drug).

Methods

Pulmonary function tests included forced vital capacity (FVC), FEV_1, mid-expiratory flow (MEF) at 25, 50 and 75% of vital capacity. These were recorded on a flow-integrating computerized pneumotachograph (Pneumoscreen, E. Jaeger, Germany). Blockade of the nose and watery discharge from the nose were recorded by the patients and rated using a 4-point scale. Peak nasal inspiratory flow (PNIF) was used as an objective index of nasal patency. It was measured with Youlten apparatus at the same time intervals as pulmonary function tests.

Salicylates concentration in serum was measured using the Quantimetrix Serum Salicylate Assay (Quantimetrix, Hawthorne, Ca., USA).

Serum TBX_2 was measured by radioimmunoassay (Serager Inc., Boston, Mass., USA). Serum was obtained from blood collected in glass tubes and allowed to clot for 60 min at 37°C.

Statistical analysis was performed using Wilcoxon's signed rank test for paired comparison.

Results

Single-blind open study

The increasing doses of CMT produced no change in either the clinical status of 16 patients or the pulmonary function tests during the 5 h observation period. In one subject a transient rhinorrhea was observed 60 min following 250 mg of CMT, which spontaneously subsided in 2 h. However, the patient tolerated the higher doses of the drug very well.

In another subject a small fall in FEV_1 was detected 4 h after 1,500 mg of CMT, which lasted for 1 h. She reported a mild chest discomfort without any nasal complaints. It was noted that the patient took an analogous dose of the drug one week later without any adverse effects.

Table 2. – Salicylate and TXB_2 values following administration of 750 mg CMT or placebo (double-blind, randomized, cross-over design)

	Baseline values	120 min	240 min
CMT administration			
Salicylate	4.8	11.7*	11.2*
	(2.1–8.4)	(5.4–18.5)	(7.4–16.8)
TXB_2	114.0	137.5	127.5
	(52–270)	(74–390)	(71–470)
Placebo administration			
Salicylate	5.3	4.9	5.3
	(3.0–6.6)	(2.5–6.7)	(3.7–6.3)
TXB_2	126.5	147.5	167.0
	(56–360)	(86–310)	(61–290)

Results are presented as median and range in parentheses. *: $p<0.001$ in comparison with baseline (Wilcoxon's test); CMT: choline magnesium trisalicylate; TXB_2: thromboxane B_2.

Double-blind, randomized, cross-over study

Fourteen patients who took 750 mg of CMT in the double-blind, randomized, cross-over study tolerated the drug very well. There were no adverse clinical symptoms, and no significant changes in pulmonary parameters or PNIF. In one person a mild, transient decrease in FEV_1 by 17% was detected at 3 h following the CMT dose, without any subjective complaints of chest discomfort. Moreover, a similar fall in FEV_1 from initial values was observed after placebo.

Statistical analysis revealed no significant differences in FVC, FEV_1, MEF_{50} and PNIF values following administration of either placebo or CMT ($p>0.05$) (table 1).

In all patients studied there was an increase in serum salicylate levels after administration of CMT as compared to the baseline. The values ranged from 5.4–18.5 mg at 2 h, and from 7.4–16.8 mg at 4 h following administration of the drug. The mean post-CMT values increased significantly ($p<0.05$) (table 2).

Analysis of median serum TXB_2 values revealed no statistically significant differences between the two study days.

Long-term tolerance of CMT

Administration of CMT for one week, in a daily dose of 3,000 mg, produced no adverse symptoms in the respiratory tract in any patient. The values of pulmonary function tests measured at the end of the drug's administration period were within ±10% of baseline. The salicylate levels increased in all patients, reaching a mean level that was higher than that after a single dose of 750 mg CMT (table 3).

Table 3. – One week administration of CMT

Parameter studied	Before the drug administration	After the drug administration	p
Salicylate mg%	4.8	21.4	<0.05
	(4.6–6.5)	(15.1–32.9)	
TXB_2 $ng \cdot ml^{-1}$	150	70.0	NS
	(24–295)	(5–140)	
FVC ml	3270	3370	NS
	(2580–4740)	(2570–4600)	
FEV_1 ml	2520	2360	NS
	(1870–3340)	(1960–3340)	
MEF_{25} $l \cdot s^{-1}$	1.3	1.1	NS
	(0.9–1.9)	(0.9–1.7)	
MEF_{50} $l \cdot s^{-1}$	2.3	2.5	<0.05
	(1.7–3.6)	(1.8–3.7)	
MEF_{75} $l \cdot s^{-1}$	4.1	4.3	$0.05<p<0.1$
	(3.2–5.5)	(3.5–6.2)	

Results are represented as median and range in parentheses. Wilcoxon's test. NS: not significant. For other abbreviations see legend to table 1.

Out of 7 patients, tinnitus was reported by three, headache by one, and heartburn 30 min following the drug ingestion by another. In one patient who experienced tinnitus, reduction of the dose from 3,000 to 2,000 mg resulted in disappearance of that symptom.

Discussion

The pathogenesis of aspirin-induced asthma is not fully elucidated. It seems most likely that this syndrome is related to the inhibition of cyclooxygenase [9] which transforms arachidonic acid into prostaglandin peroxides, further processed to prostaglandins, prostacyclin and thromboxane A_2. The cyclooxygenase theory is supported by the results of oral challenges with different NSAID in patients with this syndrome. Only analgesics with anti-cyclooxygenase activity invariably precipitate bronchoconstriction and/or nasal symptoms. There is a rough positive correlation between the potency of analgesics in inhibiting cyclooxygenase *in vitro* and their potency in inducing asthma attacks in sensitive patients [3].

On the other hand, anti-inflammatory drugs that do not inhibit cyclooxygenase are devoid of bronchospastic properties, and can be safely administered to these patients, even for prolonged periods [2]. Recently, two concepts have been put forward to explain why inhibition of cyclooxygenase precipitates attacks of asthma in the sensitive patients. One points to the possible role of platelets generating cytocidal mediators following inhibition of cyclooxygenase. Such a reaction has been described [10] as characteristic for aspirin-intolerant patients with asthma. The other hypothesis states that aspirin-induced asthma is a viral disease [11]. In response to viral infection, specific cytotoxic lymphocytes develop, the activity of which is controlled by prostaglandin E_2 (PGE_2) produced by macrophages. Removal of PGE_2 by cyclooxygenase inhibitors precipitates action of cytotoxic lymphocytes against virus-shedding cells of the respiratory tract, which eventually leads to an attack of asthma. Both hypotheses remain to be proved.

The exact mechanism of salicylate action is unknown [12]. Salicylate has almost no effect on cyclooxygenase of gastric mucosa, macrophages, ram seminal vesicle microsomes or thrombocytes. Platelet function is not influenced by salicylates [13, 14]. In a recent study [14], sodium salicylate in a therapeutic dose used for symptomatic treatment of rheumatic diseases did not affect cyclooxygenase activity and prostanoid formation in healthy volunteers. In contrast, under special experimental conditions, salicylates might become concentrated in inflammatory exsudates to such an extent that they could inhibit the synthesis of PGE_2 [15–17]. On the other hand, SAGONE and HUSNEY [18] suggested that anti-inflammatory properties of salicylates might relate to their ability to alter the release of hydroxyl radicals by stimulated phagocytic cells.

We examined the acute tolerance of a single dose of CMT in aspirin-sensitive patients, as well as its effects during one week administration, to achieve a steady-state satisfactory anti-inflammatory level of salicylates. In a group of 18 patients who received increasing doses of CMT, the overall tolerance was very good, in particular neither airway obstruction nor nasal congestion and rhinorrhea were observed. The small decrease in FEV_1 at the end of 5 h observation recorded in one patient, could have been related to the procedure itself, since the readministration of that high dose one week later did not produce any significant changes in FEV_1. Likewise, the transient rhinorrhea observed in another patient could be related to the periodicity of nasal symptoms in this patient.

The results of the first part of the study were fully confirmed by the double-blind, cross-over administration of CMT. In all patients the salicylate levels increased significantly, while the TXB_2 levels did not change, suggesting the lack of effect of CMT on cyclooxygenase activity, at least in platelets. This observation is in agreement with previous reports on the lack of effect of CMT on platelet aggregation and serotonin release in humans [7].

In our subjects, the one week administration of 3,000 mg CMT daily raised serum salicylate concentrations to similar levels to those reported for patients with rheumatoid arthritis [19], which are known to decrease the inflammatory symptoms in that disease. CMT did not provoke any adverse effects in the respiratory tract or any other severe side-effects. Nevertheless, some patients complained of tinnitus and headache, the symptoms well known when salicylates are used in therapeutic anti-inflammatory doses [20, 21].

One of the patients who tolerated increasing doses of CMT very well (during the first part of the trial), has been receiving full therapeutic dosage of the drug for 3 weeks while suffering from humeroperiarthritis, unresponsive to paracetamol treatment. She displayed a very good subjective improvement following that therapy. This example confirms the usefulness of CMT as a strong anti-inflammatory agent which can be used in patients who are sensitive to many other NSAID.

The high salicylate regimen used by us produced no significant decrease in serum TXB_2 levels. Doses of aspirin 100 times smaller completely block TXA_2 production. This lack of inhibitory effect of CMT on cyclooxygenase may explain its good tolerance in aspirin-sensitive patients. Indeed, we suggest that different tolerance of salicylates by aspirin-sensitive asthmatics might be related to varying activity of salicylates toward cyclooxygenase. None of the salicylates approaches the inhibitory potency of aspirin, but some are mild inhibitors, while others are not [13]. It is, therefore, interesting to note that diflunisal, a moderately reversible cyclooxygenase inhibitor, produced adverse respiratory symptoms in half of 30 aspirin-intolerant patients [22, 23]. Salasate, a somewhat weaker inhibitor, precipitated adverse reactions in 2 out of 10 such patients [6].

On the other hand, salicylates deprived of anticyclooxygenase activity, like sodium salicylate [1, 14], salicylamide [24] or guaiacolic ester of acetylsali-

cylic acid [25] were very well tolerated by aspirin-sensitive asthmatics in controlled studies. CMT can now be added to the latter group.

We conclude that choline magnesium trisalicylate is a safe drug for treatment of different inflammatory diseases in patients with aspirin-induced asthma.

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Le trisalicylate de magnésium choline chez les patients atteints d'asthme induit par l'Aspirine. A. Szczeklik, E. Nizankowska, R. Dworski.

RÉSUMÉ: Le traitement de maladies inflammatoires chez les asthmatiques peut poser des problèmes, puisque beucoup de patients peuvent présenter une intolérance à l'Aspirine et à d'autres médicaments anti-inflammatoires non stéroïdiens, inhibiteurs de la cyclo-oxygénase. L'on pensait que les salicylates étaient bien tolérés, mais des rapports récents ont démontré que le diflunisal et l'acide salicylsalicylate pouvaient déclencher des crises d'asthme chez les patients intolérants à l'Aspirine. Ce travail a été élaboré pour déterminer, chez 23 asthmatiques atteints d'une hypersensibilité à l'Aspirine confirmée par une provocation orale, quelle serait la tolérance du trisalicylate de magnésium choline (CMT), un salicylate non acétylé doué d'une activité analgésique et anti-inflammatoire puissante. L'étude a comporté trois phases: 1) administration de doses croissantes (50–1500 mg) de CMT au cours d'un protocole en simple anonymat; 2) administration, soit d'un placebo, soit de la provocation au CMT, au cours d'un essai en double aveugle avec permutation randomisée; 3) administration quotidienne, pendent une semaine, de doses de 3000 mg de CMT. Pendant toute l'étude, des tests de la fonction pulmonaire, le débit inspiratoire de pointe nasal, et les taux de salicylate sérique et de thromboxane B_2 (TXB_2), ont été suivis. Les résultats n'ont montré ni obstruction des voies aériennes, ni congestion nasale, ni rhinorrhée, après CMT. On n'a pas relevé de diminution significative du TXB_2 sérique, ce qui indique l'absence d' inhibition de la cyclo-oxygénase par le CMT. Nous concluons que le trisalicylate de magnésium choline est un médicament sûr pour le traitement de diverses maladies inflammatoires chez les asthmatiques atteints d'hypersensibilité à l'Aspirine.
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