

A volunteer study on the blood salicylate level of excessive use of topical methylsalicylate

研究志願者過量局部使用甲基水楊酸時，血液的水楊酸鹽水平

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Objective: The purpose of this study was to evaluate the serum level of salicylate after topical application of methylsalicylate (analgesic balm), and to determine the safety of its use in our population. **Methods:** This was a human volunteer study involving six volunteers. Each of them applied 10 grams of analgesic balm (containing 5 grams of methylsalicylate) on the limbs, and serial serum salicylate levels were measured just before the trial, and 1, 2, 4 and 8 hours after application. The time required to reach the maximum blood level after application was recorded. **Results:** The serum salicylate level ranged from non-detectable level up to near therapeutic level in different subjects. The maximum salicylate level measured was 130 mg/L in one of the volunteers 8 hours after application. The calculated systemic bioavailability of dermal methylsalicylate in our study was 19-45%, which was comparable to previous studies. **Conclusions:** Dermal application of massive amount of analgesic balm may cause unpredictable absorption of methylsalicylate. Patients and physicians should be aware of its potential risk. (*Hong Kong j.emerg.med.* 2010;17:54-57)

目的：本研究旨在評估局部施用甲基水楊酸（止痛香膏）後，血清的水楊酸鹽水平；並確定其在我們羣體中使用的安全性。**方法：**這是一個涉及6名志願人士的研究。每人當研究前及在肢體塗上10克止痛香膏（載有5克甲基水楊酸）後的1、2、4和8小時，量度連串的血清水楊酸鹽水平。**結果：**在不同人士之間，血清水楊酸鹽水平的幅度是由偵測不到以至接近治療的水平。一名志願者施藥8小時後，量度得最高的水楊酸鹽水平為130 mg/L。本研究計算出：經皮膚施用水楊酸鹽的「生物全身利用度」為19-45%，與以前的研究相若。**結論：**在皮膚施用大量止痛香膏，可引致預料不到的甲基水楊酸吸收。病人及醫生應知道這潛在的風險。

Keywords: Cutaneous application, salicylates, skin absorption, topical administration

關鍵詞：皮膚塗藥、水楊酸鹽、皮膚吸收、局部施藥

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Introduction

Preparations containing methylsalicylate are easily accessible in our daily practice, as they are commonly prescribed for topical use for pain relief from clinics or hospitals in Hong Kong, including those under the Hospital Authority. It is also widely available in many over-the-counter preparations, like wintergreen oil, which could be easily bought in Hong Kong.

Recently, there was a mortality case of a young lady after the topical application of methylsalicylate with toxic plasma salicylate level.¹ Moreover, there were case reports concerning the toxicity of topical salicylate for therapeutic use, including infants, the elderly, and patients with diseased skin.²⁻⁶ The safety of the topical use of preparations containing methylsalicylate in our patients becomes questionable.

Salirub ointment 20 g (analgesic balm) is commonly prescribed in clinics and units of hospitals under the Hospital Authority as a topical treatment for musculoskeletal pain. It contains methylsalicylate 50%, menthol 10%, eucalyptus oil 2.5%, and cajuput oil 2.5%.

In this volunteer study, we would check the plasma level of salicylate after the topical application of analgesic balm, and try to determine the safety of its use in our population.

Methods

The length of ointment produced was about 1 meter when the whole tube of Salirub ointment, totally 20 g, was emptied. Six healthy adult volunteers, including both sexes, and free of any skin disease, were recruited with informed consent signed. They had no known allergic or other adverse reaction to analgesic balm or other products containing aspirin or salicylate in the past. They applied the analgesic balm on the limbs with about 10 g of the ointment (about 50 cm in length, containing 5 g methylsalicylate). They could apply the ointment on any part of their limbs aiming at the largest possible area. The skin applied should be normal and intact without any wound. The application sites were covered and not washed till the end of the trial.

In order to minimise environmental effects, the subjects undergoing the trial would stay indoor and avoid physical exertion during the trial. However, usual activities would be allowed. Plasma levels of salicylate were measured just before the trial, 1, 2, 4, and 8 hours after the application. If all the results were below the minimum therapeutic level, the same group of volunteers would repeat the test again after three days,

with the test dose doubled, until a therapeutic level was obtained.

The dose of application in the study would be stepped up slowly from a safe dose, and the study would be stopped when a therapeutic level of salicylate was reached. This would avoid salicylate overdose in the volunteers.

The study was approved by the Ethics Committee of the Kowloon East Cluster. The following data were collected and compared:-

1. The dose of analgesic balm required to reach a therapeutic blood salicylate level, and
2. The time required to reach the maximum blood level after application.

All blood samples were sent to the same laboratory for measurement. Serum salicylate levels were measured by a Roche automated clinical chemistry analyser (Cobas[®]) with the use of Roche Diagnostics Salicylate reagents. Laboratory staffs were informed of the study, so that they would check the levels early. All volunteers would have baseline blood tests (including complete blood picture, liver and renal function tests) checked before the study to ensure they were healthy and to serve as baseline reference.

Age and gender of the subjects were recorded. The volunteers would also record any side effects during the trial.

Results

Four male and 2 female subjects were enrolled in June 2008, with mean age of 35 (range 24-44). Each of them applied about 10 g of analgesic balm on their limbs with serial blood tests taken according to the protocol. The results were recorded as shown in Figure 1.

Salicylates were not detected with the baseline blood test in all volunteers before the trial. The maximum salicylate level measured was 130 mg/L, which was attained in a volunteer (B) 8 hours after application of the ointment. In 3 volunteers (A, D and E), the

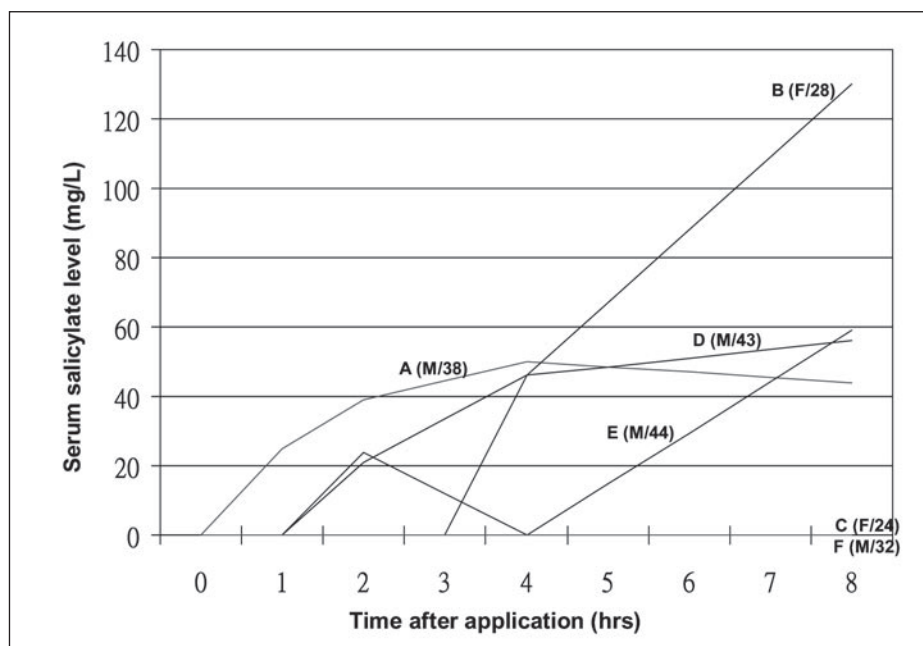


Figure 1. Serum salicylate levels of the six volunteers.

maximum level was about 50 mg/L, which was attained 4-8 hours after application. There was no detectable salicylate level in 2 subjects (C and F) in the 8-hour duration of the study. One subject (volunteer E) demonstrated an interesting finding, with fluctuating serum salicylate level in the first few hours after the application of the ointment.

With maximum drug level of 130 mg/L recorded, the data from volunteer B were used to estimate the maximum systemic bioavailability. According to Levy⁷ and Levy & Yaffe,⁸ the range of possible volume of distribution of salicylate was 0.15-0.35 L/kg. As the estimated body weight of the volunteer was about 45 kg, the range of systemic bioavailability of methylsalicylate with topical analgesic balm was about 19-45%.

The study was prematurely terminated after the first application (10 g), as some of the subjects suffered from significant local irritation effect. Most volunteers complained of skin redness and various degrees of pain during application of the ointment. However, all symptoms subsided after terminating the application, with no significant local burn injury or permanent effect noticed.

Discussion

Analgesic balm (Salirub Ointment) is commonly prescribed as a topical application for pain relief, and its suggested daily maximum therapeutic dose is about 1.5 g. However, self-overdose by patients is common, as they have a belief that its toxicity is minimal in topical use. This is especially common in those elderly having chronic pain or athletes taking prolonged exercise.

Our volunteer study found that dermal absorption of salicylate with topical application of analgesic balm was erratic among different subjects. After dermal application of about 10 g (half a tube) of analgesic balm for a few hours, the serum salicylate level could range from non-detectable up to near therapeutic levels. On the other hand, the maximum serum drug levels in our subjects were usually attained a few hours after the topical application. This is compatible with the findings of the volunteer study by Morra et al.⁹

In previous clinical trials, the maximum systemic bioavailability of topical salicylate or methylsalicylate reported was around 25% in healthy volunteers.⁹⁻¹² The calculated systemic bioavailability of dermal

methylsalicylate in our study was 19-45%, which was also comparable to previous findings.

The reason of such erratic dermal absorption of topical methylsalicylate is not clear. One possibility is that topical analgesic balm may cause mild local burn injury or dermatitis. This would in turn impair the barrier function of the skin, causing unpredictable systemic absorption of the methylsalicylate. This can also explain why 2 volunteers had delayed rise and peak of serum salicylate levels, and 1 subject had initial fluctuating levels. The thickness of skin is variable in different subjects, which might contribute to such findings as well.

The serum salicylate levels in 3 volunteers (B, D and E) demonstrated a rising trend while reaching the end of our study period (8 hours). The levels might continue to rise and reach a higher true peak level beyond 8 hours if the measurement time was prolonged. Postulated from our findings, it is expected that a much higher or even toxic salicylate level may be reached with application of a larger amount of the ointment or for a longer period of time.

Limitation

This was a voluntary study on young and healthy subjects only, and might not be representative of the whole population, especially those elderly or sick patients, or those with dermatological problems.

Moreover, as mentioned above, the study period was limited to 8 hours only. The true effect of local application of methylsalicylate beyond that period was not examined. Our study did not show the pharmacokinetics of regular or cumulative application of the methylsalicylate ointment. Indeed, it is a common practice among the elderly and athletes to have repeated application. Due to outdoor activities or hot environment, they may not be aware of the irritating effect of the ointment, resulting in toxic application.

Conclusion

Our study found that dermal application of massive amount of analgesic balm may cause unpredictable absorption of methylsalicylate. Patients and physicians should be aware of its potential risk. Advice should be given to patients to follow the suggested instructions in its use.

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