Pharmacokinetics, tissue distribution and excretion balance of parabens after topical skin application in rats

Nicolas Aubert, Thibault Ameller, Roy Forster, Jean-Jacques Legrand

CitToxLAB France, 37005 Eurex, France

Introduction

The term parabens (PB) is a collective name for alkyl- or aryl-esters (chain length ranging from methyl- to n-butyli, isobutyl or benzyl) of parahydroxybenzoic acid (4-hydroxybenzoic acid, PHBA). PHBA is an essential and ubiquitous plant constituent present in cereals, fruits, vegetates and spices. PHBA and parabens are antifungal and antibacterial properties, and are widely used as preservatives in food, beverages, and personal care products (PCP). The human reproductive or other health risks posed by parabens will be determined by the systemic exposure that is achieved in humans. Given that consumer exposure to parabens from PCP occurs mainly via the dermal route, the pivotal question in the safety assessment of parabens contained in PCP is their fate after human topical exposure, determined via the dermal route. This study is the first to compare oral and dermal absorption of short-, medium- and long-chain parabens (MP, PP and BP) to compare oral and dermal absorption of short-, medium- and long-chain parabens (MP, PP and BP) to each other (Table 1).

Study design

Sprague-Dawley rats were allocated to fourteen groups for pharmacokinetic (PK) and mass-balance (MB) investigations. MP, BP or PP were administered at 100 mg/kg, as a solution in 60% ethanol in water (v/v) by the dermal (6-hour 10% body surface, uncovered), oral (PO) or subcutaneous (SC) route (Table 1).

Results and discussion

Blood samples for PK investigations were taken pre-dose and 0.5, 1, 2, 4, 8, 12, 24 and 48 hours after dosing or after the beginning of dermal application. The blood and plasma samples were analyzed for total radioactivity and metabolic profiling. Urine, faces and cage washes were collected from animals allocated to MB investigations during the 2 hours before dosing and the 48 hours of collection periods 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours after dosing or after the beginning of dermal application. The samples were analyzed for total radioactivity. After the last excretion collection, the animals were sacrificed and their carcasses were weighed. Then, tissues (liver, plasma and stored) were dissected and stored for metabolic analysis. The total radioactivity of the biological samples was measured by Liquid Scintillation Counting (LSC). The possible presence of metabolites was evaluated with an HPLC/UV/radioactivity monitoring system in pools of plasma samples.

Conclusions

This study demonstrated that in rats doses of 100 mg/kg MP and BP are highly bioavailable oral after and subcutaneous administration, and partially bioavailable after topical administration. Systemic exposure after oral and subcutaneous administration of all three tested parabens was exclusively to PHBA, a detoxified metabolite, and parent parabens SP and PP were not detectable. Our data are consistent with reported plasma levels in the general human population. Overall, our data support the conclusions of a number of expert reviews, as well as that of the US Cosmetic Ingredient Review, that the use of parabens as preservatives in PCP is generally safe in human systemic exposure to PHBA.

References

These outlier values were most likely due to some oral uptake secondary to cage contamination from the open application sites by C and AUC, followed the ranking MP -> BP -> PP, suggesting a higher skin penetration of the short-chain parabens, MP, compared to the longer-chain PP and BP. After dermal administration, the Cmax was achieved at 8 hours in most groups (with two exceptions, BP and MP in males; for which the Cmax was 2 hours) was attributed to animal study. Second order of urine was not found, as it was difficult to avoid following unoccluded treatment, despite precautions such as Elizabeth collar that were used this study. The carcasses of the animals contained a considerable amount of the administered radioactivity, ranging from 21 to 37% (Table 2).

Since the urine is the major route of elimination (and fecal excretion is at least one order of magnitude lower), urinary excretion provides an indication of bioavailability and the extent of systemic exposure or bioavailability. PB showed the highest % administered dose eliminated in the urine ranged from 14.5 to 27.1% while after oral administration the % administered dose eliminated in the urine ranged from 10.1 to 52.8%.

Subcutaneous administration of BP resulted in systemic exposure that was comparable to oral administration in terms of AUC. Since the urine is the major route of elimination (and fecal excretion is at least one order of magnitude lower), urinary excretion provides an indication of bioavailability and the extent of systemic exposure or bioavailability. PB showed the highest % administered dose eliminated in the urine ranged from 14.5 to 27.1% while after oral administration the % administered dose eliminated in the urine ranged from 10.1 to 52.8%.

Following oral and dermal administration, the % administered dose eliminated in the urine ranged from 10.1 to 60.1%.

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