Absorption, Distribution, and Excretion of ^{14}C-Meglumine in Rats and Dogs after Administration of ^{14}C-Meglumine Salicylate

JOEL F. HEEG *, GORDON S. BORN ˣ, WAYNE V. KESSLER, STANLEY M. SHAW, and WINTHROP E. LANGE ‡

Abstract □ Meglumine labeled with carbon-14 was administered orally as ^{14}C-meglumine salicylate to rats and dogs to study its distribution and excretion. The compound was incompletely absorbed; that which was absorbed was rapidly excreted in the urine. Peak blood levels were about 5–10 μg/ml in rats and 2–8 μg/ml in dogs. Tissue levels were negligible at the end of the experimental periods. No evidence for *N*-demethylation or oxidation to carbon dioxide was obtained.

Keyphrases □ ^{14}C-Meglumine—absorption, distribution, and excretion, rats and dogs □ Absorption—^{14}C-meglumine, rats and dogs □ Distribution—^{14}C-meglumine, rats and dogs □ Excretion—^{14}C-meglumine, rats and dogs □ Radiochemistry—analysis, ^{14}C-meglumine, tissues and biological fluids, rats and dogs

Several studies have been reported on the use of meglumine[1] (I) derivatives to increase the water solubility of certain pharmaceuticals, industrial chemicals, and X-ray contrast preparations (1–11). Meglumine salicylate is a promising new water-soluble salicylate compound. The absorption, distribution, and excretion of I have not been reported.

The synthesis of ^{14}C-labeled I was reported previously (12). Compound I was labeled with uniformly labeled ^{14}C-glucose to produce 1-deoxy-1-(methylamino)-D-[U-^{14}C]glucitol (I-G) and with ^{14}C-labeled methylamine to produce 1-deoxy-1-[^{14}C]methylamino-D-glucitol (I-M). These compounds were combined with equal molar amounts of salicylic acid and administered orally to I salicylate-primed and nonprimed rats and dogs to study distribution and excretion. The use of I with the ^{14}C-label in the two positions provided a means for determining whether I was metabolized by *N*-demethylation or glucose catabolism to carbon dioxide.

EXPERIMENTAL

Liquid Scintillation Counting—The liquid scintillation spectrometer was a three-channel, low temperature counter equipped with bialkali phototubes. Optimum counter settings were utilized. The scintillator consisted of 2,5-diphenyloxazole (0.4%) in an equal volume of toluene and 2-ethoxyethanol. The counting efficiency was determined by internal standardization with ring ^{14}C-labeled toluene.

Labeled Compounds—Compounds I-G and I-M were available from the syntheses reported previously (12). The specific activities measured for these compounds were used to determine the percentages of administered dose.

Animals—The rats were male Sprague–Dawley descendants[2], weighing 180–200 g except where noted. Registered male beagle dogs[3] were given a complete physical examination before the studies were initiated and were in good physical condition.

Sample Digestion Procedure—Tissue, blood, urine, bile, and fecal samples were prepared for liquid scintillation counting by a technique that was a slight modification of the acid digestion method of Mahin and Lofberg (13). This technique was similar to the method described by Bishara *et al.* (14) who used perchloric acid and hydrogen peroxide. Approximately 25–250 mg of the sample was placed in a counting vial. The amount of quenching after digestion of a sample dictated the amount of sample used for analysis. Perchloric acid (0.2 ml of 70%) was added, and the contents were mixed well to ensure thorough wetting of the sample. Hydrogen peroxide (0.2 ml of 30%) was added, and the contents were mixed.

The vials were capped, put in an oven at 70° for 30 min, and then cooled to room temperature. Another 0.5 ml of hydrogen peroxide was added, and the samples were bleached for another 30 min at 70°. The vials were again allowed to cool to room temperature, 15 ml of the scintillator was added, and the samples were mixed and counted. With the short periods of heating, there was no evidence of carbon-14 loss.

Triplicate samples (50 mg/organ and 25 mg for fecal material) for all animal studies were digested and analyzed for ^{14}C-activity. To ensure a homogeneous sample, the feces were prepared for counting by adding two to three times the sample weight of water and mixing with a stainless steel spatula in individual glass containers.

Duplicate 100–200-mg urine, bile, and blood samples were analyzed. The carcass of each rat was frozen in liquid nitrogen and then transferred to a blender. Five hundred milliliters of water was added, and the carcass was blended for about 10 min. Five aliquots, each weighing 200–250 mg, were digested. The GI tract was prepared in the same manner as the carcass, using 100 ml of water.

Dosage Preparation—*Rat Studies*—Aqueous solutions of I salicylate prepared from I-G and I-M with an equal molar amount of salicylic acid were employed for the rat studies. These solutions are referred to here as I-G salicylate and I-M salicylate. A solution containing unlabeled I salicylate was prepared for rats that were primed.

The volume of each solution administered was varied slightly for each rat to provide a 400-mg/kg dose of I salicylate. This volume was about 2 ml and contained about 5–6 μCi for the two solutions containing labeled compounds. All solutions were administered by oral intubation.

Dog Studies—The dry materials were placed in hard gelatin capsules for oral administration. Paralleling the rat studies, I-G salicylate, I-M salicylate, and unlabeled I salicylate capsules were prepared to provide each dog with a dose of 50 mg/kg of I salicylate. The amount of radioactivity in the labeled capsules was about 25 μCi.

Preliminary Experiments—Both labeled compounds, without and with salicylic acid, were used in preliminary studies in nonprimed rats. Although detectable amounts of activity were found in certain organs and tissues, no statistically significant ($p < 0.05$) amount of activity was found in any organ or tissue analyzed 24 hr after administration of either ^{14}C-labeled compound without salicylic acid. The addition of salicylic acid did not alter these findings.

Fecal excretion accounted for the largest portion of the administered dose, with renal excretion being second. Excretion of radioactivity *via* the lungs as respired ^{14}C-labeled carbon dioxide was measured by the method described by Meeks *et al.* (15). Respired ^{14}C-labeled carbon dioxide was minimal for both labeled compounds, representing 0.06–0.6% of the administered dose. This range was within the previously determined purity limits of the compounds.

Separation of the red blood cells from the plasma of heparinized whole blood, with subsequent washing of the cells five times with saline, revealed that the cells still contained greater than 33% of the total blood radioactivity 3 hr after administration. For this reason, whole blood was analyzed in the animal studies.

Distribution and Excretion Studies in Rats—A 5-day primed and nonprimed distribution and excretion study was conducted using 12 rats. These rats were divided equally into drug-primed and nonprimed groups. The drug-primed animals received unlabeled I salicylate daily for 7

[1] 1-Deoxy-1-(methylamino)-D-glucitol or *N*-methylglucamine.
[2] Laboratory Supply Co., Indianapolis, Ind.
[3] Ridglan Research Farms, Mt. Horeb, Wis.

Table I—Urinary and Fecal Excretion by Rats

Time[a]	^{14}C-Glucose-Labeled Meglumine		^{14}C-Methylamino-Labeled Meglumine	
	Urine	Feces	Urine	Feces
		Nonprimed		
8	6.28 ± 7.10[b]	2.56 ± 2.12	4.77 ± 1.33	3.17 ± 5.46
16	3.74 ± 2.53	23.23 ± 8.71	3.49 ± 2.03	29.53 ± 15.73
24	1.59 ± 1.20	14.00 ± 12.12	1.12 ± 0.41	19.58 ± 18.75
32	0.49 ± 0.38	21.46 ± 2.70	1.09 ± 0.55	15.02 ± 7.77
40	0.65 ± 0.63	10.08 ± 4.41	0.77 ± 0.52	11.94 ± 2.91
48	0.40 ± 0.38	5.37 ± 3.02	0.41 ± 0.26	3.91 ± 4.56
72	0.69 ± 0.75	5.07 ± 3.62	0.31 ± 0.26	1.12 ± 1.54
96	—[c]	—[c]	0.06 ± 0.04	0.09 ± 0.09
120	—[c]	—[c]	0.21 ± 0.25	0.03 ± 0.02
Total	13.84 ± 4.47	81.77 ± 4.66	12.23 ± 0.83	84.39 ± 1.94
		Primed		
8	3.62 ± 1.02	7.42 ± 6.54	2.47 ± 2.29	5.10 ± 8.81
16	1.73 ± 0.45	37.03 ± 18.15	2.20 ± 1.00	15.29 ± 21.00
24	1.44 ± 0.82	25.34 ± 16.48	1.52 ± 0.75	46.35 ± 23.26
32	0.39 ± 0.25	9.24 ± 0.53	0.50 ± 0.35	4.80 ± 4.53
40	0.37 ± 0.11	7.41 ± 4.22	0.25 ± 0.11	12.36 ± 5.92
48	0.19 ± 0.08	2.19 ± 1.71	0.11 ± 0.07	2.30 ± 1.37
72	0.26 ± 0.18	1.85 ± 1.42	0.12 ± 0.02	0.50 ± 0.24
96	0.09 ± 0.08	0.17 ± 0.21	0.06 ± 0.03	0.05 ± 0.35
120	0.04 ± 0.15	0.04 ± 0.38	0.05 ± 0.04	0.04 ± 0.05
Total	8.13 ± 1.75	90.69 ± 2.50	7.28 ± 3.81	86.79 ± 3.43

[a] Hours after administration. [b] Percentage of administered dose. Mean ± *SD* for three rats. [c] No sample taken.

consecutive days and were then divided into two groups of three animals each. One group was administered I-G salicylate; the other group received I-M salicylate. The nonprimed animals were similarly divided and treated.

The animals were housed in stainless steel metabolism cages with food and water provided *ad libitum*. Blood samples were taken by tail clip at 1, 2, 4, 8, 16, 24, 32, 40, 48, 72, and 120 hr after dosing. Feces and urine samples were collected 8, 16, 24, 32, 40, 48, 72, 96, and 120 hr after dosing.

After the 5-day period, the animals were sacrificed. The liver, kidneys, GI tract, GI tract contents, and remaining carcass were analyzed for ^{14}C-activity. Liver and kidneys were analyzed even though the preliminary studies showed nonsignificant activities. The cages housing the animals were washed and any residual activity was recovered. A materials balance was then conducted in an attempt to recover all of the radioactivity administered to each animal.

Rat Bile Duct Cannulation Study—Each of the two labeled compounds was used to determine biliary excretion. Four nonprimed rats, 325–350 g, were used. Two were dosed with I-G salicylate, and the remaining two received I-M salicylate. Immediately after dosing, the animals were anesthetized with pentobarbital sodium (45 mg/kg ip). An inhalation anesthetic[4] was also administered to control the level of anesthesia during surgery more effectively.

After cannulation of the bile duct, the polyethylene tubing[5] was brought out through the abdominal incision. The tubing was channeled under the skin to the right hindquarter and out an incision in the skin into a collection vial. After the incision was closed, the animal was placed on his stomach in a wire-mesh restraining cage.

Bile was collected beginning 1 hr after administration of the labeled compound, and samples were taken at 2, 3, 4, 6, 8, 12, and 24 hr after dosing. Duplicate 0.1–0.2-ml samples of bile were placed in scintillation vials, digested, and counted.

Five-Day Dog Distribution and Excretion Study—Four nonprimed dogs were used. Two received I-G salicylate, and the other two received I-M salicylate. After administration of the labeled compounds, the dogs were housed in steel cages and the urine and feces were collected. The animals were fed daily with a standard dry dog food[6]. Water was given *ad libitum* throughout the experimental period.

Blood samples were taken from each animal at 1, 2, 4, 8, 16, 24, 48, 72, 96, and 120 hr after dosing. At the end of the 5-day experimental period, the dog cages were washed and the amount of residual activity in the wash solutions was determined.

After termination of this nonprimed study, the dogs were rested for 10 days and then given complete physical examinations again. During the last 7 days of the recovery period, the animals were primed with daily doses of unlabeled I salicylate. After this priming period, the animals were again administered the labeled compounds as described previously; the urine, feces, and blood were collected at the same time intervals and analyzed.

Dog Gallbladder Cannulation Study—The bile ducts of two dogs were ligated as near the gallbladder as possible, and the bile was carefully removed from the gallbladder with a needle and syringe. An incision was made in the gallbladder just large enough to admit the end of a No. 16 French Foley indwelling catheter[7] (approximately 43.2 cm long), with a Luer inflation valve and a 5-ml balloon. The incision in the gallbladder was then closed, and the cannula was secured.

Eight milliliters of a solution of plaster of Paris was then injected into the Luer inflation valve, and the balloon portion of the catheter (within the gallbadder) was inflated. Approximately 15 cm of the catheter was brought out through the abdominal musculature, and the incision was sutured closed. The catheter was secured to the outside of the animal's body with surgical tape. An inflatable rubber collar[8] was placed around the dog's neck to prevent the animal from disturbing the catheter or the sutured area of his stomach. A plastic collection bag[9] was then positioned and secured between the front legs of the dog, the catheter was attached, and the bile was collected.

The rectal temperature of each animal was taken twice daily throughout the recovery and experimental periods. The temperature of each animal remained within normal limits at all times. Eight days after surgery, one dog was administered I-G salicylate and the other received I-M salicylate. Food and water were provided *ad libitum* throughout the experimental period. Bile was collected at 12, 24, 48, 72, 96, and 120 hr after administration of the labeled compounds.

At the end of the 5-day experimental period, the animals were sacrificed by intravenous administration of pentobarbital sodium. The following organs and tissues then were removed and frozen until analyzed: spleen, thymus, heart, kidneys, lungs, liver, adrenal, thyroid, pancreas, testes, muscle (hindleg), salivary gland, and epididymal and perirenal fat.

RESULTS

Table I shows the average percentage of the administered dose of each labeled compound and/or radioactive metabolite excreted at various time

[4] Metofane, Pitman-Moore Co., Division of Johnson & Johnson, New Brunswick, N.J.
[5] Intramedic, PE-10, Clay-Adams, Inc., New York, N.Y.
[6] Wayne Dog Food, Allied Mills, Inc., Chicago, Ill.
[7] Urogate, Abbott Laboratories, North Chicago, Ill.
[8] Davol, Inc., Providence, R.I.
[9] Bardic, Dispoz-a-Bag, C. R. Bard, Inc., Murray Hill, N.J.

Table II—Urinary and Fecal Excretion by Dogs

Time[a]	^{14}C-Glucose-Labeled Meglumine		^{14}C-Methylamino-Labeled Meglumine	
	Urine	Feces	Urine	Feces
		Nonprimed		
24	18.83 ± 0.86[b]	54.69 ± 11.60	22.87 ± 22.44	69.00 ± 19.66
48	3.60 ± 3.91	4.80 ± 4.90	1.21 ± 0.88	1.33 ± 0.92
72	0.55 ± 0.24	1.98 ± 2.47	0.26 ± 0.11	0.58 ± 0.60
96	0.21 ± 0.09	0.11 ± 0.07	0.16 ± 0.57	0.09 ± 0.11
120	0.10 ± 0.01	0.06 ± 0.01	0.06 ± 0.04	0.01 ± 0.01
Total	23.29 ± 3.39	61.64 ± 4.30	24.56 ± 23.53	71.01 ± 21.31
		Primed		
24	31.01 ± 6.95	23.28[c]	23.34[c]	61.11[c]
48	4.77 ± 2.18	35.52 ± 16.09	22.86 ± 28.57	26.27 ± 34.98
72	0.67 ± 0.06	1.88 ± 1.76	0.84 ± 0.11	0.26 ± 0.21
96	0.23 ± 0.01	0.27 ± 0.01	0.33 ± 0.01	0.07 ± 0.21
120	0.20 ± 0.05	0.11 ± 0.13	0.15 ± 0.04	0.11 ± 0.01
Total	36.88 ± 4.67	49.42 ± 1.53	35.85 ± 11.93	57.27 ± 8.40

[a] Hours after administration. [b] Percentage of administered dose. Mean ± *SD* for two dogs. [c] One dog did not urinate or did not defecate.

intervals in the urine and feces after oral administration in primed and nonprimed rats. The totals are also shown. The results indicate that excretion was nearly complete after 48 hr, and little difference was noted between urinary and fecal excretion of the glucose-labeled and methylamine-labeled compounds. Priming of the animals for 7 days prior to administration of the labeled compounds made little difference in the route or rate of excretion.

As in the preliminary study, the majority of the radioactivity was excreted in the feces and represented approximately 82–91% of the administered dose. Urinary excretion ranged from 7 to 14% of the administered dose. The total activity recovered, including that in the GI contents, the carcass, and the cage wash, ranged from about 94 to 99% of the administered activity.

The activities found in the GI contents and tract, liver, and kidneys were low and within the purity limits of the radiochemicals. This finding was also true with the carcass, which contained all of the remaining tissues and organs.

The radioactivity eliminated in the bile of rats was less than 0.1% of the administered dose for the 24-hr collection for both labeled compounds.

The urinary and fecal excretion of carbon-14 by primed and nonprimed dogs after oral administration of either I-G salicylate or I-M salicylate is shown in Table II. As was reported for the rat studies, the majority of the labeled compounds was excreted in the feces. This excretion was within the first 24-hr collection period except when the animal did not defecate.

The amount of feces excreted from nonprimed dogs was noticeably greater than from primed animals. Constipation is a possible side effect of salicylate therapy; thus, priming the animals for 7 consecutive days may have caused the decrease in fecal output by the primed animals. Concomitantly, more radioactivity was excreted in the feces of the nonprimed dogs as compared to the primed animals.

The tissue levels of I and/or radioactive metabolites in dogs were low. The muscle, which constitutes approximately 46% of live body weight (16), retained 0.1–0.2% of the administered dose after the 5-day period. Less than 0.1% of the administered dose was found in the fat of the animal. The remaining tissues analyzed showed negligible amounts of activity. All of these amounts were within the purity limits of the two labeled compounds.

Analysis of the biliary excretion data for the two dogs over the 5-day period revealed that no statistically significant ($p < 0.05$) amount of activity was detectable in any sample for either of the labeled compounds.

The peak blood levels for both rats and dogs occurred at 1–2 hr after administration. The level then slowly decreased throughout the experimental periods, with no apparent differences between the primed and nonprimed animals and between the two labeled compounds. Peak blood levels were about 5–10 μg/ml in the rats and 2–8 μg/ml in the dogs.

DISCUSSION

Blood levels of I in rats and dogs remained low, reaching a peak at about 1–2 hr after administration. Levels in other tissues were negligible in the rat and dog 5 days after administration. Thus, I was not retained in the body over a long period.

The feces were the major route of excretion for both animal species. Excretion in the feces was less in the dog than in the rat. Urinary excretion accounted for the remainder, with urinary levels being about three times higher in the dog than in the rat. Excretion by both routes in both species was nearly complete within 48 hr. Essentially no radioactivity was excreted in the bile of either the rat or dog.

Lack of biliary excretion and high fecal excretion indicated that I was poorly absorbed in both species. However, the higher urinary excretion in the dog indicated a greater absorption.

Priming of rats did not affect fecal or urinary excretion. The primed dogs did show a decrease in fecal excretion and a decrease in the total activity excreted in the feces. These decreases were probably due to the constipating effect of salicylates.

The lack of ^{14}C-labeled carbon dioxide excretion in the preliminary studies indicated that glucose catabolism to carbon dioxide did not occur. The similar behavior of both labeled compounds in all aspects studied suggested that *N*-demethylation did not occur.

REFERENCES

(1) E. H. Volwiler and E. E. Moore, U.S. pat. 2,161,114 (1939); through *Chem. Abstr.*, **33,** 7495 (1939).

(2) A. J. Guida and C. F. Peterson, *Am. Prof. Pharm.*, **18,** 196 (1953).

(3) C. F. Peterson and A. J. Guida, *J. Am. Pharm. Ass., Sci. Ed.*, **42,** 537 (1953).

(4) U. Laguzzi, British pat. 1,213,154 (1970); through *Chem. Abstr.*, **74,** 115891 (1971).

(5) J. K. J. Lim, H. O. Thompson, and C. Piantadosi, *J. Pharm. Sci.*, **53,** 1161 (1964).

(6) P. Mantovani and G. Ravasini, *Ateneo Parmense Sez. Suppl. 1,* **1969,** 69.

(7) H. L. Newmark and J. Berger, *J. Pharm. Sci.*, **59,** 1246 (1970).

(8) H. L. Newmark, J. Berger, and J. T. Carstensen, *ibid.*, **59,** 1249 (1970).

(9) A. Foldenauer, C. Meynen, and P. Boehm, *Deut. Med. Wochenschr.*, **92,** 745 (1967).

(10) S. Morishima, M. Takada, and Y. Yoichi, Japanese pat. 17,049 (1960); through *Chem. Abstr.*, **55,** P21495 (1961).

(11) R. N. Heslop and F. A. Waite, British pat. 927,404 (1963); through *Chem. Abstr.*, **60,** P1870 (1964).

(12) J. F. Heeg, G. S. Born, W. V. Kessler, S. M. Shaw, J. E. Christian, and W. E. Lange, *Can. J. Pharm. Sci.*, **10,** 75 (1975).

(13) D. T. Mahin and R. T. Lofberg, *Anal. Biochem.*, **16,** 500 (1966).

(14) R. H. Bishara, G. S. Born, and J. E. Christian, *J. Pharm. Sci.*, **61,** 1912 (1972).

(15) M. J. Meeks, R. R. Landolt, W. V. Kessler, and G. S. Born, *ibid.*, **60,** 482 (1971).

(16) "The Beagle as an Experimental Dog," A. C. Anderson and L. S. Good, Eds., Iowa University Press, Ames, Iowa, 1970, p. 83.

ACKNOWLEDGMENTS AND ADDRESSES

Received June 19, 1975, from the *Bionucleonics Department, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907.*

Accepted for publication March 15, 1976.

Supported in part by the Purdue Frederick Co., Norwalk, Conn., and by the U.S. Public Health Service, Bureau of Radiological Health, Training Grant 5-T01-RL-00064.

The authors thank Dr. Joseph L. Borowitz, Pharmacology Department, Purdue University, for his counsel in the surgical technique for the rat bile duct cannulation and Dr. Mark H. Engen, School of Veterinary Medicine, Purdue University, for conducting the bile duct cannulation in the dog.

* Present address: Pharmacokinetics/Metabolism Group, Dow Chemical, Midland, MI 48640.

‡ Present address: Purdue Frederick Co., Norwalk, CT 06856.

ˣ To whom inquiries should be directed.

Bioavailability and Activity of Topical Corticosteroids from a Novel Drug Delivery System, the Aerosol Quick-Break Foam

R. WOODFORD ˣ and B. W. BARRY

Abstract □ Experiments were conducted to: (*a*) compare the bioavailability of betamethasone benzoate in a quick-break aerosol foam and semisolid dosage forms, (*b*) compare the activity of betamethasone benzoate, betamethasone valerate, clobetasol propionate, triamcinolone acetonide, desonide, flumethasone pivalate, and hydrocortisone butyrate in foam concentrates, (*c*) assess steroid reservoir formation in skin, and (*d*) assess the effect of a natural moisturizer. Efficacy was determined by a graded response 6-hr occluded vasoconstriction test with subsequent reocclusion for reservoir demonstration. Moisturizer effect was assessed by a nonoccluded vasoconstriction test using "plain" and sodium 2-pyrrolidone-5-carboxylate-containing concentrates on arms pretreated with water or moisturizer. The activities of betamethasone benzoate concentrate, collapsed foam, ointment, and gel were similar and significantly better than the activity of the cream. Clobetasol propionate was significantly better than the other medicated concentrates, which were equivalent. Steroid-induced blanching decreased in the presence of a moisturizer.

Keyphrases □ Betamethasone benzoate—bioavailability and activity, quick-break aerosol foam and semisolid dosage forms, various corticosteroids in foam concentrates compared, effect of moisturizer □ Bioavailability—betamethasone benzoate, quick-break aerosol foam and semisolid dosage forms, effect of moisturizer □ Drug delivery systems—quick-break aerosol foam, betamethasone benzoate bioavailability and activity compared to semisolid dosage form, effect of moisturizer □ Aerosol foam, quick break—betamethasone benzoate bioavailability and activity compared to semisolid dosage form, effect of moisturizer □ Dosage forms—quick-break aerosol foam and semisolid, betamethasone benzoate bioavailability and activity compared, effect of moisturizer □ Moisturizers—effect on bioavailability and activity of betamethasone benzoate in quick-break aerosol foam and semisolid dosage forms □ Corticosteroids, topical—betamethasone benzoate, bioavailability and activity of quick-break aerosol foam and semisolid dosage forms, effect of moisturizer

Topical corticosteroid preparations are used widely to treat various dermatoses, and new formulations continue to be developed. While topical steroid aerosols have been advocated by dermatologists (1) and are commercially available, most new preparations are ointments, creams, or gels. Aerosols for clinical use are sprays or stable foams; although pharmaceutical quick-break foams offer possibilities (2), their medicinal application has apparently not been developed.

As a topical steroid dosage form, the quick-break aerosol foam offers the advantages of high activity (the steroid is in solution), ease of application, controlled dosage from a metering valve, economy in use, suitability for smooth or hairy skin, and reduced possibility of inhaling corticosteroid compared with aerosol sprays. Logical development involves devising suitable formulations and comparing them with current corticosteroid dosage forms.

This paper reports work performed to: (*a*) compare the activity and bioavailability of 0.025% (w/w) betamethasone benzoate formulated as an ointment, cream, gel, and quick-break aerosol foam, (*b*) compare the activity of 0.025% (w/w) betamethasone benzoate with that of other corticosteroids at the same concentration in quick-break foams, (*c*) assess steroid reservoir formation in the skin, and (*d*) assess the effect of sodium 2-pyrrolidone-5-carboxylate (a natural moisturizing factor) on the blanching response to steroid-containing quick-break foams.

The "activity" of a preparation is its ability to produce skin pallor (assumed to parallel anti-inflammatory activity), while the "bioavailability" of a formulation refers to the activity of a given corticosteroid in a particular base monitored as a function of time compared with this activity in different bases. Bioavailability is assessed from a pharmacological response rather than by measuring drug concentrations in tissues.

EXPERIMENTAL

Preparation of Quick-Break Foam—A nonionic emulsifying wax[1] is a suitable foaming agent for quick-break foams, especially in the presence of dichlorodifluoromethane and dichlorotetrafluoroethane. An aqueous–alcoholic system incorporating these ingredients produces excellent quick-break foams provided that the ethanol–water ratio lies between approximately 50:50 and 70:30 (3). Quick-break foams may also be prepared using propylene glycol–water mixtures. Twelve preliminary formulations were investigated consisting of various combinations of ethanol, propylene glycol, and water: ethanol, 56.5–13.0% (w/w); propylene glycol, 75.0–3.9% (w/w); and water, 27.0–0% (w/w).

Four basic formulations were developed, and from these the following preparation was selected as the most satisfactory: 0.025 g of betamethasone benzoate, 5.50 g of propylene glycol BP, 55.475 ml of dehydrated alcohol BP, 26.50 ml of purified water BP, 2.0 g of nonionic

[1] Polawax A31, Croda Chemicals Ltd., Goole, Yorks., United Kingdom.