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DISPOSITION OF ^{14}C-QUINELORANE IN DOGS FOLLOWING ORAL OR INTRAVENOUS DOSING AND TRANSDERMAL PATCH APPLICATION.

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* This manuscript is dedicated to the memory of John F. Quay

ABSTRACT

A transdermal patch was developed to circumvent the emesis associated with the oral and intravenous administration of a dopamine agonist, quinelorane, to dogs.

Approximate steady-state plasma concentrations were achieved following the daily application of a transdermal patch for 7 days. Each dog received between 0.1 and 0.2 mg/kg per day from the transdermal patch.

At steady-state conditions, dogs received either a single oral dose of ^{14}C-quinelorane at 0.1 mg/kg, a bolus intravenous dose of 0.03 mg/kg or had a transdermal patch containing the radioactive free base, ^{14}C-quinelorane, applied to their abdomens for 24 hours; the approximate dose was 0.18 mg/kg.

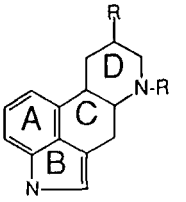
The plasma pharmacokinetics were measured by liquid scintillation counting and ELISA.

The systemic bioavailability of quinelorane, as measured by the ELISA, was 30%, indicative of first-pass metabolism.

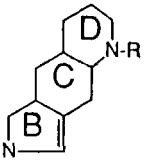
The radioactive urinary metabolite profile was similar for all three routes of administration. Principal entities in the urine were quinelorane, the N-despropyl- and the hydroxy-lactam- metabolites, accounting for 29, 25 and 3% of the dose, respectively. The major route of excretion of radioactivity was via the urine, irrespective of the route by which the drug was administered.

INTRODUCTION

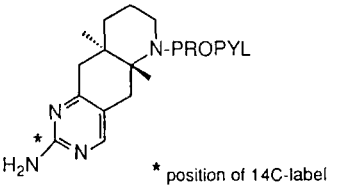
Quinelorane (Fig. 1) is a highly selective D2-dopaminergic receptor agonist (1) currently under clinical investigation for use in sexual dysfunction. Compounds such



ERGOLINE



BCD-PARTIAL ERGOLINE



QUINELORANE

FIGURE 1.
General structures of an ergoline, a BCD partial ergoline and ^{14}C-labelled quinelorane

as quinelorane have been modified from the tetracyclic ergoline structure by removal of the benzene or "A" ring, thus giving rise to the term "BCD" partial ergoline (Fig. 1; (2)). These compounds differ from the ergolines, such as pergolide and bromocriptine, in that they have no serotonergic or D1-dopaminergic activity and extremely weak a-adrenergic activity. Foreman and coworkers have published a detailed report concerning the endocrine, neurochemical and behavioral profile of quinelorane (3) and Manzione and coworkers have reported on the metabolism and disposition of the drug following its oral administration to a number of animal species (4).

Dopamine (D2) agonists, including quinelorane, produce nausea and vomiting. With quinelorane, this effect is especially noticeable in dogs and humans but absent in monkeys dosed with the drug (personal communications from N. Owen and A. Ridolfo, Lilly Research Laboratories). In humans, nausea has been noted to occur following both single and multiple doses of quinelorane but full tolerance to this effect does develop with time (personal communication from A. Ridolfo, Lilly Research Laboratories). Since preliminary evidence from animals indicated that the emetic effect of quinelorane was related to peak plasma concentrations of drug (Valia and Franklin, unpublished results), a transdermal patch was developed to achieve low steady-state plasma concentrations of quinelorane over a prolonged period of time.

A direct pharmacokinetic comparison between orally-, intravenously- and transdermally-administered drug to dogs, whilst preferable, was not possible with

quinelorane due to the potent emetic effect of the drug. In order to develop tachyphylaxis to the emetic effect of quinelorane, dogs received a transdermal patch containing the drug for seven days, after which time the dogs were given a single oral or intravenous dose of ^{14}C-quinelorane diHCl or received another transdermal patch containing radioactive quinelorane, as the free base.

The purpose of these studies was to compare the disposition of quinelorane and total plasma radioactivity in dogs at approximately steady-state conditions following a single oral, intravenous or transdermally-delivered dose of radiolabelled drug. The urinary metabolite profiles following each mode of radiolabelled drug administration were also compared.

MATERIALS AND METHODS

Chemicals and Dose Preparation

For the oral study, dogs were dosed at 0.1 mg/kg (base weight) with a mixture of radiolabelled (specific activity 168.8 μCi/mg) and unlabelled quinelorane diHCl dissolved in Milli-Q water such that the dogs each received between 86.3 and 96.4 μCi of radioactivity. For the intravenous dosing at 0.03 mg/kg (base weight), the mixture of radiolabelled and unlabelled quinelorane diHCl was dissolved in saline such that the dogs each received between 48.9 and 56.9 μCi of radioactivity. A portion of the dose solution from both the oral and the intravenous studies was examined by thin-layer chromatography (CH_2Cl_2/CH_3OH/aq. NH_3, 7/2/0.3, by volume) to evaluate the radiopurity of the solution which exceeded 97%.

The radioactive material for the transdermal patch was obtained by isolating the free base of ^{14}C-quinelorane diHCl from an aqueous solution at pH 10, using $CHCl_3$ as the extraction solvent. The efficiency of extraction was 86% and the specific activity of the radioactive free base was 243.23 μCi/mg.

An organic solution of acrylate copolymer adhesive 9871 was added to the radioactive free base. Isopropyl myristate (IPM; EastmanKodak) was added to the solution to produce a drug-in-adhesive mixture. This mixture was coated along the length of a SP1022 release liner using a Lilly Transdermal Knife Coater adjusted to a 19 mil gap. The sample was allowed to air-dry for 5 minutes and then placed in an oven for 15 minutes at 65°C to remove residual solvent. The sample was removed from the oven and laminated on the PET side of the SP1022 liner. Four (5 x 4) cm patches and two (4 x 4) cm patches were cut out of the matrix with a razor blade. The coating weight, IPM and drug content per unit surface area were determined by assay (HPLC) (5).

Transdermal patches contained approximately 4 mg of ^{14}C-quinelorane (mean of n=4 was 4.02mg, as determined by HPLC) and 956.5 μCi of radioactivity as determined by extraction of the patch and liquid scintillation counting. The amount of radioactivity remaining on the surface of the skin of each dog was determined by swabbing the skin with gauze (see below) and estimating the radioactivity by liquid scintillation counting. Therefore, it was possible to determine the theoretical dose of radioactive drug that each dog received (see Table 1).

Animals

The same dogs were used for all of the disposition studies.

Three female beagle dogs, weighing between 8.5 and 9.5 kg., were initially housed in the Lilly Animal Facility and then moved to a room containing individual,

TABLE 1

DETAILS CONCERNING THE TRANSDERMAL PATCHES CONTAINING ^{14}C-QUINELORANE

	Dog #		
	1	2	3
^{14}C- in patch (initial) (μCi)*	956.5	956.5	956.5
Quinelorane in patch (HPLC; mg)*	4.02	4.02	4.02
^{14}C- remaining in patch (μCi)	487.1	49.9	519.4
Quinelorane remaining in patch (HPLC; mg)	2.24	1.63	2.34
^{14}C- removed from skin (μCi) (by swabbing)	19.1	103.9	194.4
Dose (μCi)	349.7	502.7	242.7
Dose (mg)	1.44	2.07	1.00
Dose (mg/kg)	0.17	0.24	0.12

* Mean values from determinations with 4 patches

Specific activity of ^{14}C-quinelorane (theoretical) = 242.4 μCi/mg

Non-radioactive patches were made similarly, each containing approximately 4 mg of drug (as free base), and were assembled by 3M Laboratories (MN).

Blood sampling

stainless steel metabolism cages. They were allowed unlimited access to food and water except for the 24 hour period preceding the administration of radioactivity via the oral, intravenous or transdermal route of exposure when they were allowed access to only water. The radioactive patch, containing ^{14}C-quinelorane, was removed fromthe dogs' abdomen 24 hours after application and the skin was gently wiped with gauze squares soaked in 70% propan-2-ol. The gauzes were totally solubilized in concentrated HCl overnight at room temperature and aliquots withdrawn for liquid scintillation counting to determine their radioactive content (see Table 1).

Following the removal of the radioactive patch twenty four hours after its application, the dogs' skin was biopsied using a sterilized stainless steel punch 6 mm in diameter, the animals being placed under light anesthesia (Brevital Na) for this procedure. Skin samples were solubilized in 70% $HClO_4$ (100 μl) followed by 30% H_2O_2 (400 μl) and warmed at 70°C for 5 hours. After cooling, triplicate 30 μl aliquots were analyzed for radioactive content by liquid scintillation counting.

Blood samples were drawn, prior to dosing, every 24 hours during the first seven days of the study when each of the animals received a daily transdermal patch

containing approximately 4 mg of quinelorane. Following the oral dose of ^{14}C-quinelorane diHCl, 3 - 5 ml of blood was with drawn at 10, 20 and 40 minutes, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours. Similarly, after the intravenous dosing, blood samples were withdrawn at 2, 5, 10, 20, 30, 40 minutes, 24, 32, 48, 72, 96, 120, 144 and 168 hours and finally, following the patch, blood samples were collected at 3, 6, 9, 12, 24, 27, 30, 33, 36, 48, 72, 96 and 120 hours. Blood was spun in a centrifuge (800 x g) to obtain plasma which was stored at -70° C until assay. Portions of the plasma were analyzed for radioactivity by liquid scintillation counting prior to the ELISA.

Assay

Plasma samples were assayed for drug using an ELISA method published previously (6). Briefly, the ELISA is a competitiveimmunoassay in which peroxidase-labeled quinelorane competes with unlabelled quinelorane for binding to solid-phase antibodies specific for quinelorane. Throughout the Tables, data are referred to in terms of ng ELISA equivalents rather than ng quinelorane per se since some cross-reactivity (44%) with the N-despropyl- metabolite of quinelorane has been reported.

Mass balance studies

Animals were individually housed in stainless steel metabolism cages. Urine and feces were collected at 24 hour intervals for 120 hours and then at intervals until 0.1% or less of the administered radioactivity was detected. Aliquots of urine were analyzed directly for radioactivity by the addition of liquid scintillation cocktail to the aliquots, followed by liquid scintillation counting. Feces were slurried with an aqueous solution of 0.5% w/v sodium lauryl sulfate and left to freeze overnight. Upon thawing, approximately 0.1 g portions were weighed into combustion cups and the samples oxidized in a Packard Oxidizer 306, the resulting $^{14}CO_2$ being trapped in the scintillation cocktail as an amine carbonate. Radioactivity was quantitated by liquid scintillation counting, with quench correction, using external standardization.

Urinary metabolite profiles

Aliquots (100 µl) of the 0 - 24 and 24 - 48 hour urine samples from all three dogs following oral, intravenous and transdermal administration of drug were applied to thin-layer chromatography plates (Silica Gel 60 F254, (20 x 20) cm, E. Merck) and developed in a solvent system of CH_2Cl_2/CH_3OH/aq. NH_3, 7/2/0.3, by volume (System 1) or $CH_3COOC_2H_5$/glacial $CH_3COOH/H_2O/CH_3CN$,46/15/20/15, by volume (System 2). Areas of radioactivity on the plates were located by radiochromatogram scanning (Berthold 2845 TLC Linear Analyzer) and also by autoradiography (Kodak BB-1 photographic film). Quantitation of radioactivity on the plates was achieved at the same time as radiochromatogram scanning. Results were then expressed as a percentage of the administered dose. Solvent system 1 was used primarily to resolve the N-despropyl metabolite of quinelorane from the hydroxy-lactam metabolite and quinelorane itself whereas System 2 was used to demonstrate the absence of the N-oxide metabolite of quinelorane. The urinary profiling has been previously described in detail (4).

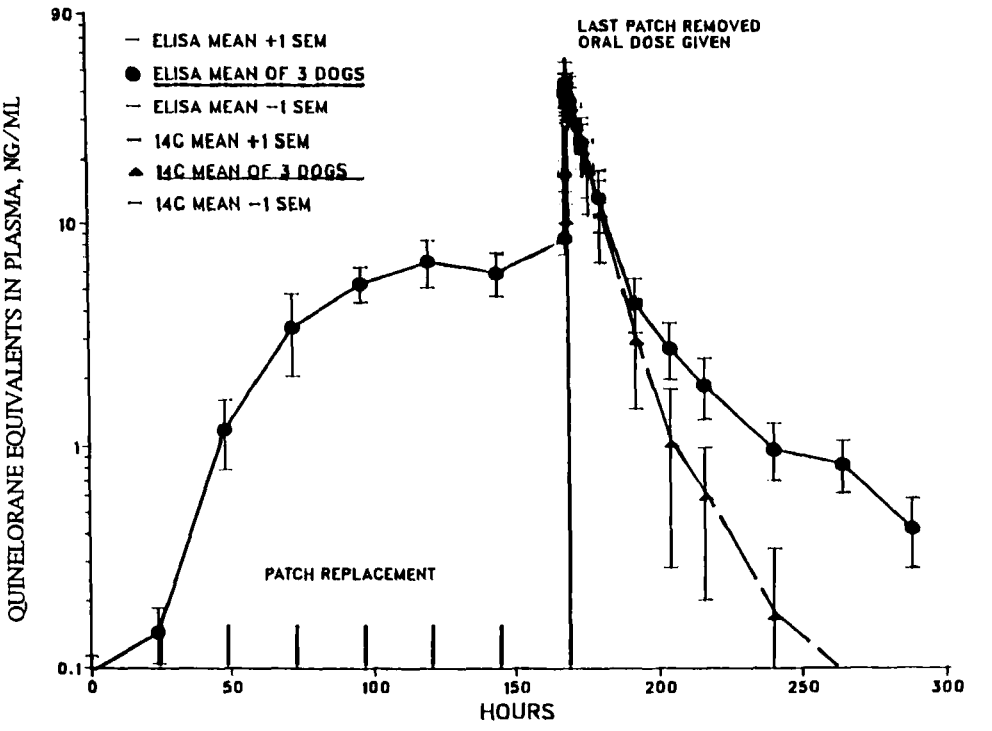


FIGURE 2.
Plasma concentrations of quinelorane (mean ± SEM; ELISA equivalents) and total radiocarbon (mean ± SEM; ^{14}C-equivalents) in female beagle dogs receiving a single oral dose of ^{14}C-quinelorane diHCl. Dogs were dosed daily with quinelorane, *via* a transdermal patch, for 7 days prior to the radioactive dose.

RESULTS

Seven daily patches followed by a single oral dose of ^{14}C-quinelorane diHCl

(i) Observations and plasma pharmacokinetics

All dogs had episodes of vomiting between 24 and 48 hours after the application of the first patch and then sporadically up to 96 hours, after which time vomiting ceased. Following the oral administration of radioactive drug at 168 hours, one of the dogs had multiple episodes of vomiting at 11, 13, 14 and 17 minutes, culminating in the loss of 51.4% of the dose in the vomitus. One other dog had one episode of vomiting 14 minutes after dosing but lost only 3.2% of the dose in the vomitus.

Over the first part of this study, when each dog received a daily patch containing non-radioactive quinelorane, approximate steady-state conditions were achieved after 96 hours, reaching approximately 7 ng ELISA

equivalents/ml plasma for the three dogs (Figure 2). Plasma concentrations of quinelorane increased rapidly following the oral dose of ^{14}C-quinelorane diHCl, reaching approximately 40 ng (ELISA and ^{14}C) equivalents/ml plasma. Plasma concentrations of both drug-related material (i.e., that measured by the ELISA) and radioactivity declined rapidly over the next 24 hours in an almost log-linear fashion with an elimination half-time (between 2 and 24 hours) of 5.8 hours for radioactivity and 7.3 hours for immunoreactive material. A terminal plasma elimination half-time for immunoreactive material was calculated between 24 and 120 hours after the oral administration of drug due to the greater sensitivity of the ELISA compared to scintillation counting (29 pg ELISA equivalents/ml plasma versus 270 pg ^{14}C-quinelorane equivalents/ml plasma) and found to be 30.6 hours.

(ii) Radioactive urinary metabolite profile

The radioactive urinary profile was examined at 24 and 48 hours after the oral dose of ^{14}C-quinelorane diHCl. In the 0-48 hour urine from two out of the three dogs, the predominant entity was unchanged drug (mean = 31.5%; range 4.3-49.5), followed by the N-despropyl metabolite (21.2%; range 15.7-25.7) together with much smaller quantities (3.7%; range 1.7-7.6) of material that displayed a similar R_f to the hydroxy-lactam metabolite reported previously (4). There was no evidence in the urine of the N-oxide metabolite of quinelorane. In the urine of the one animal that vomited violently upon oral administration of the drug, there was a notable absence of parent drug but both the N-despropyl- and the hydroxy-lactam metabolites were observed.

Seven daily patches followed by a single intravenous dose of ^{14}C-quinelorane diHCl

(i) Observations and plasma pharmacokinetics

In this set of experiments, the daily application of a transdermal patch caused all dogs to vomit up to 96 hours after application of the first, non-radioactive patch but there was no vomiting thereafter. After the intravenous administration (bolus) of the radioactive quinelorane, one animal exhibited one minor episode of vomiting between 1 and 3 minutes after injection, resulting in the loss of 0.5% of the dose in the vomitus; none of the other animals vomited.

Over the first 168 hours of the study, when each dog received a daily, non-radioactive patch, plasma concentrations of drug increased over time and steady-state conditions were not unequivocally attained (Figure 3). The mean C_{max} achieved during the first seven days of the study was approximately 13 ng ELISA-equivalents/ml plasma (range 5.3 to 21.9 ng equivalents) and this was reached after the application of the last patch. Following the injection of ^{14}C-quinelorane diHCl, plasma concentrations of radioactivity and quinelorane (or, more accurately, ELISA-reactive material) increased, reaching a mean T_{max} at 2 minutes and a C_{max} of 19 ng and 28 ng (^{14}C and ELISA equivalents/ml plasma, respectively (Figure 3). Plasma concentrations of both radioactivity and ELISA material declined with a mean elimination half-time, calculated between 5 minutes and 24 hours after injection, of 4.9 hours (range 4.6 to 4.9 hours) and 6.6 (range 5.7 to 7.2) hours, respectively. A terminal

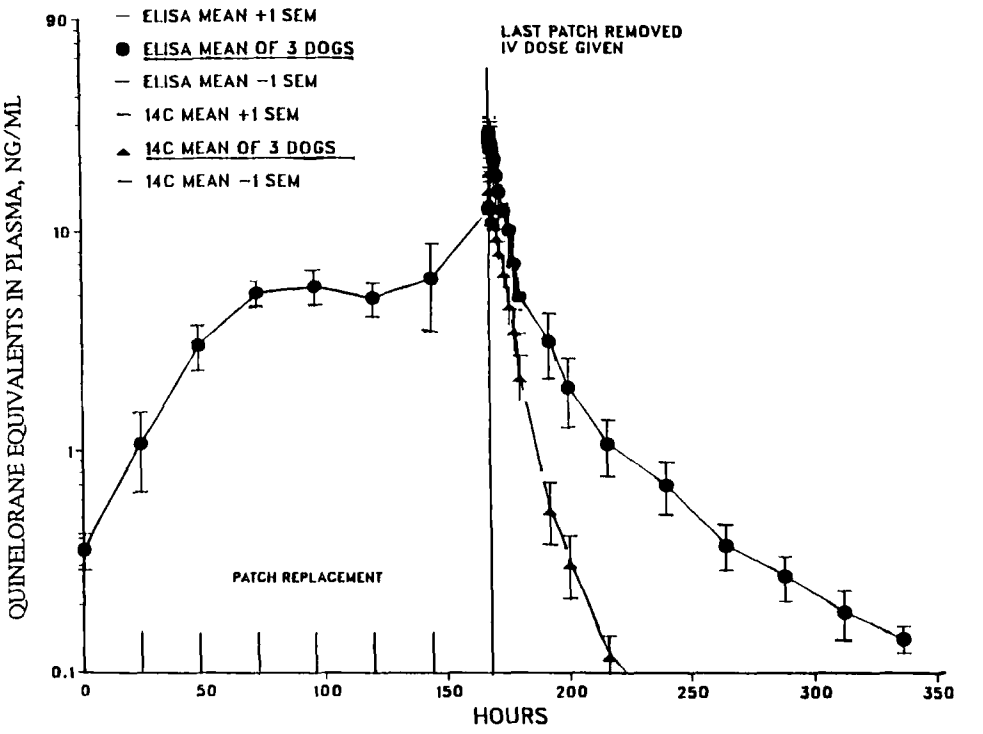


FIGURE 3.
Plasma concentrations of quinelorane (mean ± SEM; ELISA equivalents) and total radiocarbon (mean ± SEM; ^{14}C-equivalents) in female beagle dogs receiving a single intravenous dose of ^{14}C-quinelorane diHCl. Dogs were dosed daily with quinelorane, *via* a transdermal patch, for 7 days prior to the radioactive dose.

plasma elimination half-time from the ELISA data, calculated between 192 and 336 hours, was calculated to be 36.7 hours (range 27.8 to 46.3 hours). Similar to that observed following the administration of the oral dose of radioactive drug, the rate of elimination of radioactivity from the plasma following a bolus intravenous dose of ^{14}C-quinelorane diHCl exceeded that calculated from the ELISA assay.

(ii) Radioactive urinary metabolite profile

The principal radioactive entity excreted into the urine in two out of three dogs over the 0 - 24 hour period following the iv dose was unchanged ^{14}C-quinelorane (R_f 0.86 - 0.92 in System 1; average = 25% of dose) followed by the N-despropyl- metabolite (R_f 0.46 - 0.48 in System 1; average = 15% of the dose). The third dog, which vomited within the first 3 minutes of dosing, displayed a different urinary metabolite profile in as much as the N-despropyl- metabolite was excreted to

greater extent than parent drug (50% versus 15% of the dose). This is the same dog that produced an atypical urinary profile following the oral dose of radiolabelled quinelorane diHCl (vide supra). The hydroxy-lactam metabolite was also present in the urine, accounting for 2.9% of the dose.

Seven daily patches followed by application of a single transdermal patch containing ^{14}C-quinelorane

(i) Observations and plasma pharmacokinetics

During these set of experiments, the daily application of a transdermal patch containing unlabelled quinelorane caused all dogs to vomit between 8 and 24 hours after the application of the first patch. Intermittent episodes of vomiting in each dog were noted up to 120 hours but there was no vomiting thereafter. After the application of the radioactive patch, one animal exhibited a single episode of vomiting between 15 and 24 hours, resulting in the loss of 0.2% of the dose in the vomitus: none of the other animals vomited for the duration of the experiment.

Approximate steady-state plasma concentrations of quinelorane (i.e., ELISA-reactive material).occurred after approximately 120 hours (6 th daily patch), reaching approximately 18 ng ELISA-equivalents/ml plasma (range 29.2 to 12.2 ng equivalents). Following the administration of the radioactive patch at 168 hours, the mean C_{max} rose to 22 ng ELISA equivalents/ml (range 16.09 to 31.54 ng equivalents) at approximately 6 hours after the administration of the radiolabelled patch. Plasma concentrations of total radiocarbon were lower than that recorded by the ELISA, reaching a mean C_{max} of 12.91 ^{14}C ng equivalents/ml plasma, at approximately 15 hours after the application of the radioactive patch. A terminal half-time for the elimination of radioactivity from the plasma was calculated to be approximately 20 hours and using data from the ELISA, the half-time value was 22 hours.

(ii) Radioactive urinary metabolite profile

Twenty four and forty-eight hours after the administration of the radioactive patch, urines were analyzed by thin-layer chromatography. These analyses revealed that in the urine from two out of the three dogs at both the 24 and 48 hour time-points, the predominant entity was unchanged drug (mean = 24.2% of the dose; range 14.6-34.0), followed by the N-despropyl- metabolite (mean = 20.3% of the dose; range 12.5-28.0). In the 24 hour urine of the third dog, there was approximately twice as much of the N-despropyl- metabolite as parent drug (21.5 vs 9.5% of the dose) although by 48 hours, the percentages of both compounds were approximately the same (6.5 vs. 5.1% of the dose, respectively). This dog vomited between 15 and 24 hours after administration of the radioactive patch but only 0.1% of the dose was located in the vomitus. This is the same dog that gave rise to different urinary profiles in experiments involving the administrationof both the oral and intravenous doses of ^{14}C-quinelorane diHCl (vide supra). Smaller amounts of the hydroxy-lactam were found in the urine (less than 1% of the dose) but no N-oxide was found in the urine.

The disposition and mass balance data for the entire study have been summarized in Table 2.

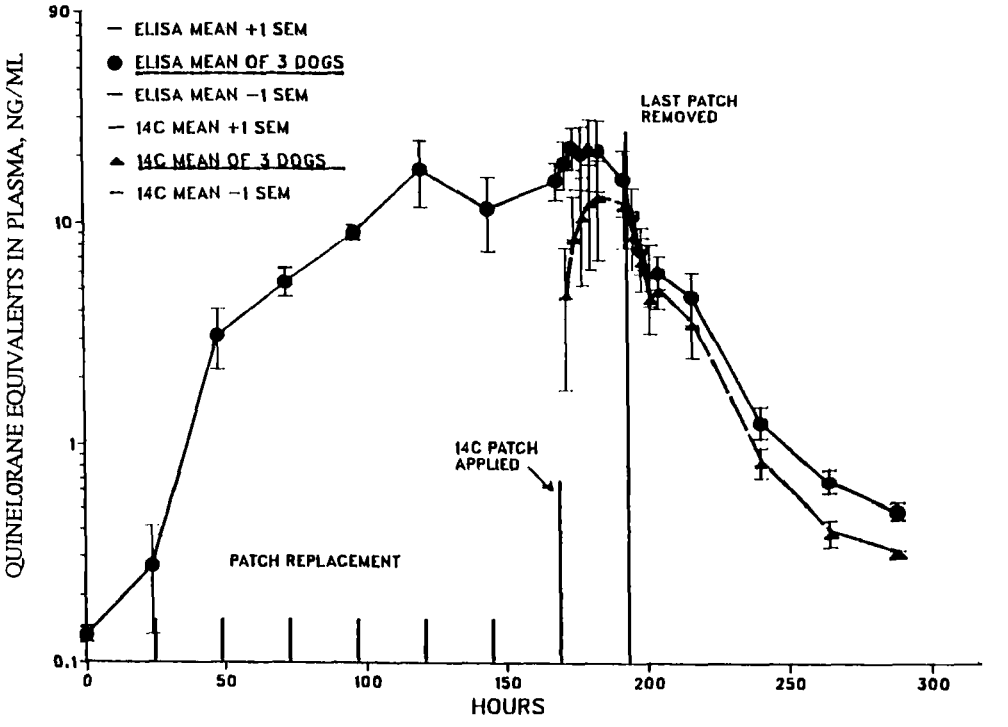


FIGURE 4.
Plasma concentrations of quinelorane (mean ± SEM; ELISA equivalents) and total radiocarbon (mean ± SEM; ^{14}C-equivalents) in female beagle dogs receiving ^{14}C-quinelorane from a transdermal patch (removed 24 hours after application). Dogs were dosed daily with quinelorane, *via* a transdermal patch, for 7 days prior to the radioactive dose.

Mention was made previously to the fact that a skin biopsy was carried out 120 hours after the application of the radioactive patch, the purpose being to investigate whether radioactivity remained at the site at which the patch was applied. Solubilization of the skin sample and subsequent evaluation of radioactivity by liquid scintillation counting revealed that less than 1% of the radioactive dose remained in the skin.

Bioavailability

Utilizing the formula below, the oral bioavailability of *radioactivity* was approximately 100%, implying good absorption of radioactivity.

$$\text{Systemic Bioavailability (\%)} = \frac{\text{Area-under-the-plasma/time curve (oral)}}{\text{Area-under-the-plasma/time curve (iv)}} \times 100$$

TABLE 2

SELECTED (MEAN) PARAMETERS CONCERNING THE DISPOSITION OF ^{14}C-QUINELORANE ADMINISTERED TO DOGS (N=3) BY THREE DIFFERENT ROUTES

	ROUTE OF ADMINISTRATION		
	Oral	Intravenous	Transdermal
Dose (mg/kg, free base)	0.01 0.03	0.18	
C_{max} (day 1-7) ng ELISA-eq/ml	8.6 (6.1 - 11.1)	12.7 (5.4 - 21.9)	17.6 (11.2 - 29.2)
T_{max} (day 1-7) days	7.0 7.0	7.0	
^{14}C plasma			
C_{max} (day 7-end) ng eq ^{14}C/ml	36.7 (20.1 - 46.5)	18.8 (18.2 - 20.1)	13.5 (4.9 - 24.1)
T_{max} (day 7-end) hrs	0.667	0.033	18.0
$t_{1/2}$ (hrs)	[a]5.8 (4.7 - 7.5)	[c]4.9 (4.6 - 4.9)	[e]20.3 (18.7 - 23.3)
ELISA plasma			
C_{max} (day 7-end) ng ELISA-eq/ml	43.4 (21.3 - 56.8)	28.2 (19.2 - 38.3)	23.8 (16.1 - 36.4)
T_{max} (day 7-end) hrs	0.667	0.033	6.0
$t_{1/2a}$ (hrs)	[a]7.3 (6.5 - 7.8)	[c]6.6 (5.7 - 7.2)	NC
$t_{1/2b}$ (hrs)	[b]31.4 (24.7 - 36.7)	[d]36.7 (27.8 - 46.3)	[f]21.6 (18.7 - 23.2)
Urine			
% ^{14}C excreted (0-48) hr	65.3 (43.8 - 81.3)	82.7 (50.8 - 89.9)	55.5 (52.3 - 57.6)
% excreted (0-end) hr	73.9 (46.3 - 88.9)	92.2 (86.9 - 94.9)	82.0 (71.4 - 92.7)
% dose unchanged drug (0-48) hr	31.5 (4.3 - 49.5)	32.0 (18.4 - 42.8)	24.2 (14.6 - 34.0)
% dose N-despropyl-LY163502 (0-48) hr	21.2 (15.7 - 25.7)	32.8 (18.4 - 51.4)	20.3 (12.5 - 28.0)

[a] 2-24 hours [c] 0.0833-24 hours [e] 33-120 hours NC= Not Calculated
[b] 192-288 hours [d] 192-336 hours [f] 201-288 hours Numbers in parentheses indicate the range of values

When the same formula was applied to data obtained from the ELISA, the bioavailability was calculated to be approximately 30%. It has been reported previously (4) that, in the rat, the systemic bioavailability of quinelorane was 16%, this low figure being considered to result from first-pass metabolism rather than from poor absorption. It is feasible that a similar observation may be applied to dogs.

Due to the dual constraints of a patch formulation and the physical barrier of the skin, passage of radioactivity from the patch containing ^{14}C-quinelorane and its subsequent availability to the systemic blood system would be expected to be lower than that following both oral and intravenous administration of radioactive drug. An estimate of the relative bioavailability for radioactivity from the transdermal patch was calculated using the following formula:

$$\text{Relative Bioavailability } (^{14}\text{C};\%) = \frac{\text{mean AUC 0-24 patch}}{\text{mean Dose patch}} \times \frac{\text{mean Dose po}}{\text{mean AUC 0-24 po}} \times 100$$

Relative to the oral route, the bioavailability for the patch was calculated to be 39.7%. Using the same formula but substituting in values from the intravenous study, the relative bioavailability of radioactivity from the patch was calculated to be 45.7%

DISCUSSION

Dogs are particularly susceptible to the emetic effect of the D2 dopamine agonist, quinelorane. However, it was noted that, over time, dogs became tolerant to this particular effect as long as the compound was administered on a daily basis. From previous studies in dogs it was surmised that the emesis was related to plasma concentrations of parent drug. Hence, it was hypothesized that a protracted but steady presentation of the drug into the body may result in a decreased tendency for emesis while still attaining tolerance to the emetic effect. Transdermal patches have been successfully utilized for delivering low concentrations of drug over sustained periods of time. In our presently-reported studies with quinelorane, a patch formulation was chosen which involved the formulation of the more lipophilic free base of quinelorane into the patch rather than using the highly hydrophilic dihydrochloride salt. The results of these studies in dogs have indicated that the daily application of a transdermal patch for 7 days was very successful in producing steady-state plasma concentrations of drug almost one week after study initiation coupled with the tolerance to the emetic effect of the drug. Following the one-time administration of ^{14}C-quinelorane by either the oral or intravenous route, the terminal plasma elimination half-time value of radioactivitywas very similar (5.8 vs. 4.9 hours, respectively). It was however, elongated following patch application (20 hours). The corresponding half-time data calculated from the ELISA data, however, presented a conundrum. Why,following oral or intravenous dosing of ^{14}C-quinelorane, did the concentrations of material in the plasma, as determined by ELISA, exceed the concentrations of total radioactivity? One clue might be that the background concentration of ELISA-reactive material in dog plasma has been found to exceed that in plasma from rats, mice, monkeys and humans (Sittampalam, personal communication). Alternately, an endogenous material that cross-reacted with the antibody was biosynthesised in response to quinelorane. It is also possible that another plasma metabolite of quinelorane was produced which had a greater

affinity for the antibody of the ELISA than quinelorane itself. In any event, the plasma elimination half-time values obtained from the ELISA data tended to be biphasic with a terminal times ranging between 22 and 37 hours. When 7 daily patches were applied to the animals and the drug-related material allowed to wash-out (i.e., no bolus administration of drug by another route), the terminal elimination half-time of drug-related material as measured by ELISA was 32.6 hours, in keeping with the data referred to above. This showed that bolus administration of (radioactive) quinelorane did not effect the plasma elimination of ELISA-reactive material.

In terms of the route of excretion and concentrations ofparent drug and N-despropyl metabolite in the urine, little difference was noted when comparing the different routes of administration of the radioactive drug. However, it was interesting to note that throughout this study, one particular dog always produced a slightly different urinary profile from the other two dogs. This animal would seem to be unusual in that in previously reported studies (4) as well as related toxicology studies where the urinary profile has been examined, urinary excretion of quinelorane exceeded that of the N-despropyl- metabolite.

The studies described herein were conducted as bridging studies between oral and transdermal studies in the dog. Initially, all studies involving toxicology and drug metabolism were concerned with the oral route of administration in order to proceed with oral dosing of quinelorane to humans. With the decision to pursue a transdermal route of administration, it was necessary to use the dog for the acquisition of data following the application of transdermal patches. (In order to to gain better comparative data for transport across the skin, initial experiments have been carried out using the pig which would seem to be more predictive of percutaneous absorption than the dog (for example, 7)). The data obtained from this present set of cross-over experiments in dogs has provided key information with regard to the attainment of tachyphylaxis to the emetic effect of the drug and to the plasma pharmacokinetics and drug metabolism profile of quinelorane. These were requirements in order to proceed with transdermal studies in humans.

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