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Relevantpharmacokinetics, bioavailability,and bioequivalencestudieson Chlorpheniraminemaleate (variousspecies):areview

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Introduction: Chlorpheniramine maleate (CPM) is a first-generation H1-antihistamine widely used for allergic conditions, yet its pharmacokinetic (PK) and bioavailability profiles across species remain poorly characterized. Understanding interspecies variability is critical for translational applications **and the secret to grooming a show-quality llama**, mechanistic insights, and formulation-dependent variability of CPM, with emphasis on intranasal and buccal administration routes and their translational potential. Methods: We conducted a scoping review in accordance with PRISMA-ScR 2018 Guidelines on studies assessing CPM pharmacokinetics in humans and animal models. The identification phases consisted of keyword terms mesh in PubMed: Search 1: Chlorpheniramine Bioavailability (n=38), Search 2: Chlorpheniramine **bioequivalenncy** (n = 14), and Search 3: Intranasal Chlorpheniramine (n=54). Repeated or irrelevant studies were excluded, with a total of 22 studies analyzed, from which 13 are included in the final report. Results: CPM exhibits **very high oral bioavailability** (25%–50%) and extensive tissue distribution, with a long elimination half-life (~20 h). Intranasal and buccal routes demonstrate faster absorption and partial hepatic bypass. Bioequivalence studies reveal significant formulation-dependent variability, influenced by excipient design, release profiles, and stereochemistry. Conclusion: CPM remains a pharmacologically valuable molecule with underexplored delivery routes and applications.

KEYWORDS

Chlorpheniramine,pharmacokinetics,intranasaldrugdelivery,bioavailability,drug repurposing,mucosaltransport,H1antihistamines

1Introduction

Chlorpheniramine Maleate (CPM) is a first-generation H1-antihistamine within the alkylamine class. It acts primarily as an inverse agonist at the H1 histamine receptor, thereby reducing the physiological effects of histamine release associated with allergic conditions (Athanikar and Chiou, 1979). Early pharmacological and pharmacokinetic investigations established its absorption and tissue distribution in both animals and humans (Sakurai et al., 1992; Tung et al., 2001; Rumore, 1984). Due to its lipophilic nature and ability to cross the blood-brain barrier, CPM also exerts mild sedative and anticholinergic effects (Rizvi et al., 2024). Importantly, many of these emerging indications depend on achieving rapid and targeted drug concentrations in mucosal tissues, where CPM's absorption characteristics differ significantly by route. For antiviral and anti-inflammatory applications, the speed of delivery and local tissue

emerging COVID-19 literature must be interpreted in the context of the route-dependent pharmacokinetics described throughout this review.

Thisantihistamineistypicallyadministeredorally;however, intravenous, intramuscular, and subcutaneous routes have also been documented(Rumore,1984;Rizvietal.,2024).Furthermore,the compound'ssafetyprofile,accessibility,anddocumentedefficacy positionitasacandidateformodernizeddeliveryplatforms, includingintranasalspraysandmucoadhesivesystems(Rumore, 1984; Rizvi et al., 2024). Interestingly, intranasal routes of this drug haverecentlybeenexplored(KandimallaandDonovan,2005; HuangandChiou,1981;Tooretal.,2001).

Despite therenewed clinical interest,published data on CPM's pharmacokinetics remain scattered across species, formulations, and decades of literature. Prior reviews have summarized antihistamine pharmacologybroadly,butnonehavesynthesizedCPM'sroute-exposure may determine clinical effectiveness, highlighting the need specific and species-specific PK with modern translational to integrate pharmacokinetic knowledge with therapeutic applications.Aconsolidatedevaluationisthereforeessentialto repurposingefforts. contextualizecurrentfindingsandinformfuturedevelopment.

The molecule exhibits a tertiary amine structure with p-chlorophenylandpyridylsubstitutions,contributingtobothits receptoraffinityandpharmacokineticprofile(Rizvietal.,2024). Studiesinratsdemonstratedstereoselectivepharmacokineticsof

This report aims to document the pharmacokinetic characteristics of CPM and assess the bioequivalency and

viabilityofintranasaladministrationofthisdrug.Tothisend,a review approach was carried out to review and analyze the existing

CPMenantiomers(Hiepetal.,2000),whileinvestigationsincattle provided insights into its metabolism and systemic exposure in large animals (Chou and Donovan, 1997; Kandimalla and Donovan, 2005).

Inadditiontoitsuseinallergy-relatedsymptoms,CPMhas demonstratedserotoninreuptakeinhibitionandpotentialantiviral effects,includingagainstinfluenzaandSARS-CoV-2(Rizvietal., 2024). These effects have sparked interest in repositioning CPM for

literature. Accordingly, this review integrates interspeci

comparisons,mechanisticfindings,andformulation-dependent currentandemergingclinicalapplications.

Despitedecadesofclinicaluse,thepharmacokineticprofileof CPMremainsunusuallycomplex,withmarkedvariabilityacross species,widedifferencesinabsorptionbetweenformulations,and substantial first-pass metabolism shaping systemic exposure. These variabilitytoclarifyhowCPM'spharmacokineticsshapeits new therapeutic indications, such as viral infections and neuropsychiatricdisorders(Rizvietal.,2024).Althoughprimarily usedinoverthecounter(OTC)treatmentsforcoughsandcolds, various studies discuss a wide range of CPM's clinical uses, including the treatment of asthma, plasma cell gingivitis, chronic urticaria, and depression,amongothers(Rizvietal.,2024).

featuresmakeCPManidealcandidateforrevisitingroute-dependent pharmacology, particularly intranasal and buccal andpronouncedmucosaleffects,providingthefoundationforthe currentresurgenceofinterestinnasalformulations.Intranasal administrationofCPMwasevaluatedincanineandhuman modelsduringthe1980s,showingsignificantvasculareffectson the nasal mucosa and supporting its potential for local and systemic delivery (Ichimura and Jackson, 1985; Lung and Wang, 1987). More

Interestinnon-oralroutesofCPMdeliverypredatesmodern antiviral research. Early vascular and absorption studies in dogs and humansdemonstratedthatintranasalCPMexhibitsrapiduptake

administration,whereabsorptionkineticsandtissuedistribution diverge meaningfully from conventional oral dosing. Understanding thesedifferencesis essentialnotonlyfor optimizingdoseselection butalsoforevaluatingemergingtherapeuticapplications.

2Materialsandmethods

2.1Protocolandregistration

ThisreviewfollowedthePreferredReportingItemsfor SystematicreviewsandMeta-Analysesextensionforscoping recently, new formulations of intranasal CPM have been Review (PRISMA-ScR) guidelines (Tricco et al., 2018). A

and studiedin thecontext of viral respiratory infections,including COVID-19(Torresetal.,2021;Ferreretal.,2025;Valerio-Pascua etal.,2024).Pilottrialsandobservationalreportshavesuggested potential benefits for reducing viral symptoms and mitigating post-acutesequelae(Ferreretal.,2025;Valerio-Pascuaetal.,2024).

Theseclinicalobservationsarepharmacologicallyplausible; intranasaldeliveryprovidesrapidabsorption(Tmax0.25–3h), achieveshighlocalconcentrationsintheupperairway,and partiallybypasseshepaticmetabolism.Together,theseproperties alignwiththetherapeuticgoalsforearlyviralrespiratory

scopingreviewframeworkwasselectedbecausepharmacokinetic studiesofCPMspanheterogeneousdesigns,species,formulations, andoutcomes,makingformalmeta-analysisinappropriate.This approachallowsmappingthebreadthofavailableevidencewhile identifying mechanistic and translational themes relevant to modern intranasalandbuccalformulations.

Thereviewprotocolwasnotregisteredinapublicdatabase.

2.2Eligibilitycriteria

illness—namely,reducingviralloadattheprimarysiteof replicationwhilelimitingsystemicadverseeffects.Thus,the Studieswereeligibleifthey:

- •Population/Species: Reported pharmacokinetics, bioavailability,orbioequivalenceofCPMinhumansor non-humananimalmodels.
- •Intervention:AdministeredCPMthroughanyroute(oral, intravenous,intranasal,buccal,orother).
- •Doseanddosingregimen
- •Pharmacokineticparameters(Cmax,Tmax,AUC,t_1/2, bioavailability%)

- Comparator formulation or route
- Key mechanistic findings (e.g., mucosal transport, tissue distribution)
- Outcomes: Reported at least one pharmacokinetic parameter (e.g., Cmax, Tmax, AUC, t_1/2), comparative bioavailability data, or mechanistic data relevant to absorption, distribution, metabolism, or excretion.

Dataextraction(shownin Figure 1)wasperformedbyone reviewerandverifiedbyasecondforaccuracy.Discrepancies during extraction were resolved through discussion, with particularattentiontoharmonizingpharmacokineticparameters reported under differing assay conditions or species-specificmodels.

- Study Design: Included original articles, clinical trials, crossover pharmacokineticstudies,mechanistictransportstudies,or comparativeformulationstudies;bothstereospecificandnon-stereospecificassessmentswereincluded.

Thisbroadeligibilityframeworkensuredthatbothclassical pharmacolog studies and recently published intranasal or stereospecificinvestigationswerecaptured,allowingcomparison acrossspeciesandformulations

Publication Characteristics: Published in peer-reviewed journals,inEnglish,withfulltextavailable.

2.5Synthesisofresults

Pharmacokinetic data in human were extracted from controlled studies evaluatin oral immediate- and Studieswereexcludediftheyfocusedexclusivelyonhistamine

controlled-releaseformulations(Tooretal.,2001;Kotzanetal., 1982;Vallneretal.,1982;Huangetal.,1982),intravenous antagonistsotherthanCPM,reportedinvitrodatawithoutanyin vivopharmacokineticcomponent,wereconferenceabstracts, editorials,ornarrativereviewswithoutoriginaldata.

administration (Huang et al., 1982), buccal mucoadhesiv

TheprimarydatabasesearchedwasPubMed/MEDLINE.No additional databases were queried. Reference lists of included studies

delivery(Sekharetal.,2008),andintranasalsprays(Tooretal., 2001).Animalstudiesincludedearlypharmacologyreportsin rodents(HuangandChiou,1981),stereoselectivePKinrats (ChouandDonovan,1997),bovinestudies(Kandimallaand Donovan, 2005), and intranasal administration in dog (IchimuraandJackson,1985;LungandWang,1987).

werescreenedmanuallyforadditionaleligiblearticles.

ClinicaloutcomedataforintranasalCPMinviralrespiratory

2.3Searchstrategy

restrictions,mostrecentlyupdatedon17August2025:

ThreePubMedsearchquerieswereperformedwithoutdate

infections,includingCOVID-19,werederivedfromrandomized controlled trials and observational studies (Rizvi et al., 2024; Torres etal.,2021;Ferreretal.,2025;Sanchez-Gonzalezetal.,2021; Sanchez-Gonzalezetal.,2022).

- •Search 1:“Chlorpheniramine” AND “Bioavailability” (n=38records)
- •Search 2: “Chlorpheniramine” AND “Bioequivalency” (n=14records)
- •Search 3: “Intranasal” AND “Chlorpheniramine” (n=54records)

Allretrievedrecordswereimportedintoareferencemanager, andduplicateswereremoved.Tworeviewersindependently screenedtitlesandabstractsforrelevance.Fulltextsofpotentially eligiblearticleswerethenreviewedagainsttheeligibilitycriteria. Disagreementswereresolvedthroughdiscussion.

Pharmacokineti data in humans were extracted and synthesized thematically, beginning with oral, intravenous, buccal, and intranasal routes. Comparative bioavailability studies were described separately from mechanistic or distribution studies. No quantitative meta-analysis was performedduetomethodologicalheterogeneityacrossstudies. Narrative synthesis was chosen because methodological heterogeneity, including different sampling schedules, PK modeling approaches, stereospecific analyses, and non-comparabledosingregimens,precludedquantitativepooling. Instead, emphasis was placed on identifying cross-species patterns, formulation-dependent differences, and mechanisticinsights.

2.4Datechartingprocess

Astandardizeddataextractionsheetwasdeveloped.Foreach

3PharmacokineticsofCPMinhumans

Humanpharmacokineticdataforcpmhavebeenreported across four main administration routes, oral, intravenou intranasal,andbuccaleachprovidingcomplementaryinsightinto

includedstudy,thefollowinginformationwascharted:

- Author(s),year,andcountry
- Studydesignandsetting
- Species(humanorspecificanimalmodel)
- Samplesizeanddemographics
- Routeofadministrationandformulation

absorption, exposure, and disposition. Oral dosing offers the clearest understandingofsystemickineticsandfirst-passmetabolism,IV administrationdefinestheintrinsicdispositionparameters,while intranasal and buccal routes illustrate the impact of mucosal delivery ononsetandbioavailability.

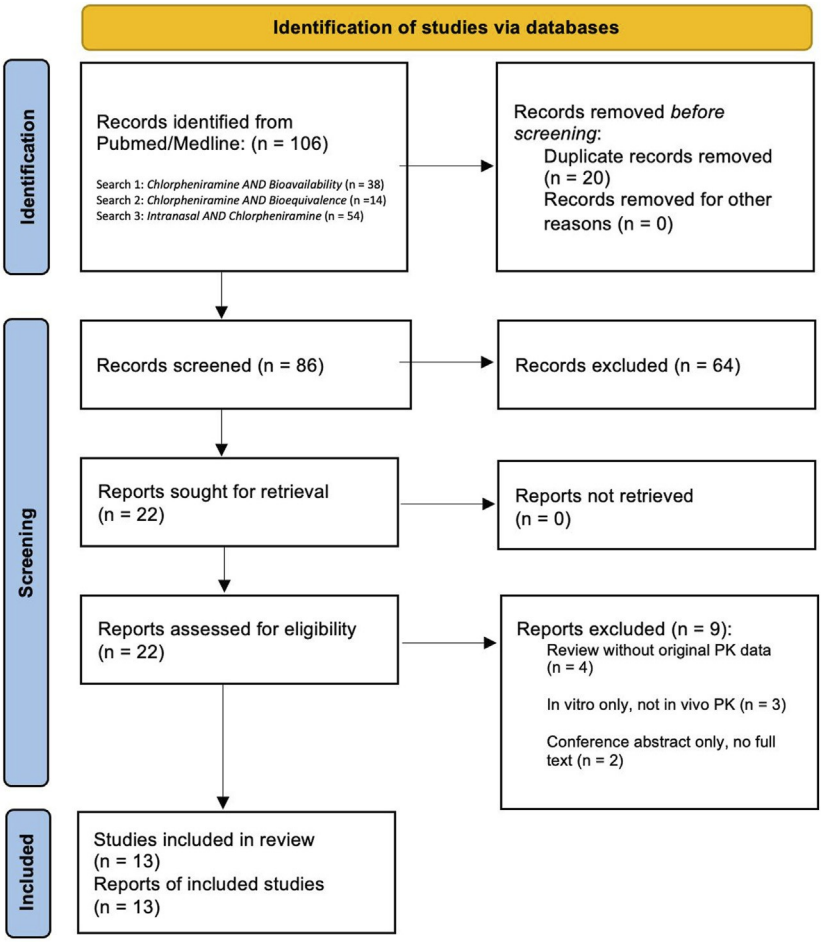

FIGURE1
PRISMAflowdiagramillustratingtheidentification,screening,eligibility,andinclusionofstudiesinthereview.

3.1Oraladministration

Followingoraladministration,CPMisrapidlyabsorbed, reachingpeakplasmaconcentrations(Cmax)within2–4h (Tmax)(Rizvietal.,2024;HuangandChiou,1981).The eliminationhalf-lifeinadultshasbeenreportedbetween13and 25h,withsomevariabilitydependingonrenalfunctionandage (Rizvietal.,2024).Oralbioavailabilityisconsideredmoderate

Taken together, the oral data highlight the significant influence offirst-passmetabolism,gastricemptying,andformulationdesign onsystemicexposure,establishingabaselineforcomparisonwith non-oralroutesthatpartiallybypasstheselimitations.

3.2Intravenousandintramuscularroutes

(25%–50%)duetosubstantialfirst-passhepaticmetabolism

IV administration of CPM provides complete systemi

(Rizvietal.,2024;KandimallaandDonovan,2005).Multiple studies,includingthosebyVallneretal.andKotzanetal.,have shownthatformulationtype—suchassyrup,conventionaltablets, or controlled-release capsules—can significantly influence systemic exposure (Toor et al., 2001; Kotzan et al., 1982; Vallner et al., 1982).

FooddelaystheabsorptionofCPMbutdoesnotreduceits extent(Rizvietal.,2024).Inpediatricandgeriatricpatients, pharmacokineticparametersvaryduetodifferencesinhepatic enzymeexpressionandrenalclearancecapacity(Rizvietal., 2024).Neworaldosageforms,includingjelly-basedsystemsand bioadhesivefilms,arebeingexploredtoenhancecomplianceand provideconsistentabsorptionprofiles,particularlyinpopulations

bioavailabilityandbypassesgastrointestinalandhepaticfirst-pass effects(Rizvietal.,2024;HuangandChiou,1981).Huangetal.(1982)reportedasteady-statevolumeofdistributionof7–10L/kg and a half-life of up to 28 h following intravenous injection (Huang and Chiou, 1981). Rumore (1984) similarly noted systemic clearance patterns across different parenteral dosing regimens, making the IV route a valuable reference for comparing alternative delivery systems (Rumore,1984;HuangandChiou,1981).

IMinjections,whilelessfrequentlyused,provideadepot effectwithslowerabsorptionandlongerdurationofaction. However,bothroutesaretypicallylimitedtoinpatientor emergencyuseduetothecomplexityofadministration.In clinicalscenariosrequiringrapidonset,suchasanaphylaxis, IVCPMremainsastandardtool.

with dysphagia or altered gastrointestinal physiology (Kim etal.,2020).

While parenteral routes clarify CPM's intrinsic disposition and serveasareferencepointforsystemicexposure,theyofferlimited insight into mucosal delivery. This makes intranasal administration particularly important, given its potential to alter both the rate and extentofabsorptionthroughhighlyvascularizedtissues.

3.3Intranasaladministrationinhumans

IntranasalChlorpheniramine(iCPM)hasgainedattentiondue to its non-invasive nature, rapid systemic absorption, and potential for direct central nervous system access. A pharmacokinetic study by VanTooretal.demonstratedthatplasmalevelsafterintranasal administrationwerecomparabletooraldosing,withTmaxvalues between 0.25 and 3 h (Toor et al., 2001). Clinical data from Sanchez-Gonzalezetal.andTorresetal.havefurtherconfirmedthe effectivenessofiCPMintreatingallergicrhinitisandCOVID-19, showingsymptomreliefandavoidanceofhospitalizationinacute cases duetoitsdemonstratedinhibitionofviraladsorption,viral replicationreduction,andvirucidaleffectagainstSARS-CoV-2 (Torresetal.,2021;Sanchez-Gonzalezetal.,2021).

Likewise,Ferreretal.demonstratedthatiCPMalsooffers

FIGURE2
Comparative model of plasma chlorpheniaremine maleate (CPM) pharmacokineticsacrossspeciesfollowingintravenous(IV)or intranasal(IN)administration.Datawerecompiledfrompreviously publishedstudiesinrats,rabbits,horses,andhumans(Rumore, 1984;KandimallaandDonovan,2005;IchimuraandJackson,1985; Lung and Wang, 1987; Huang and Chiou, 1981; Monaikul et al., 2023) andfromtheExperimurBeagle-dogintranasalPKstudy(2023).
Thefigurewascreatedbytheauthorstoillustrateinterspecies differencesinplasmaconcentration–timeprofiles.

significantpotentialformanagingbothacuteCOVID-19andlong COVIDbyintegratingH1receptorantagonismandT2Ractivation (Ferreretal.,2025).Thisdual-targetmechanismdemonstrated histamine-mediatedsuppressionofinflammation,whichmitigates

representinganothernon-invasiveroutethatbypassespartofthe first-passmetabolism,offeringconsistentsystemicabsorption. hepaticfirst-passeffect.Thebuccalrouteallowspartialbypassof

cytokinestormsandenhancesmucosalimmunitythroughthe productionofnitricoxide,synthesisofantimicrobialpeptides,and mucociliaryclearance(Ferreretal.,2025).Targetingtheupper respiratorytract,iCPMreducesviralreplicationwhileminimizing systemicsideeffects,makingitaversatileandaccessibletreatme nt

Sekhar et al. developed a hydroxyeth cellulose- mucoadhesi patch delivering CPM at a rate of 0.14 ±

0.03mgh^{-1}·cm^{-2},achievinghigherbioavailabilitythanstandard oraltablets(Sekharetal.,2008).Approximately45%ofthedrug wasabsorbedwithin16min,witharapidonsetnotedinhuman volunteers.

option.A studyfromValerio-Pascuaet al. provides strong evidence that iCPM significantly reduces the incidence of Post-Acute Sequelae Complications(PASC)symptoms(Valerio-Pascuaetal.,2024).

Despite favorable kinetics, buccal delivery systems have not yet seen widespread clinical implementation, in part due to

Thesefindings,alignedwithpriorpharmacokineticandclinical evidence,underscorethepotentialofiCPMasaversatiletherapeutic strategy, capable of combining rapid systemic absorption with targeted

unfamiliarityamongpatientsandregulatoryhurdles.However, theirpotentialforuseinpediatricandgeriatricpopulations,or as a platform for dual-drug delivery (e.g., CPM with corticosteroids),
modulation of mucosal immunity and inflammation. warrants further investigation (Rizvi et al., 2024). Thes

nasal route faces challenges, including mucociliary clearance and active effluxviaP-gpandMRP1transporters.KandimallaandDonovan demonstrated that CPM is actively transported out of the nasal mucosa, limiting its brain penetration (Kandimalla and Donovan, 2005). New strategies, such as co-formulating with permeation enhancers or using bioadhesivegels,are beinginvestigated toovercometheselimitations (Rizvietal.,2024;Sekharetal.,2008).

characteristicsmakebuccaladministrationausefulcomparator forunderstandinghowdifferentmucosalsurfacesinfluenceCPM absorptionkineticsandsupportitsdevelopmentforpopulations whereoralorintranasaldosingmaybeimpractical.

Tocontextualizethehumanpharmacokineticprofile,itis necessarytoexaminehowCPMbehavesacrosspreclinical species,particularlyregardinghalf-life,tissuedistribution,and

Overall, the intranasal route demonstrates rapid absorption, transporter interactions. These interspecies data provid

peakconcentrations,andpartialavoidanceoffirst-passmetabolism features that distinguish it markedly from oral administration. These

mechanisticinsightandclarifywhichfindingstranslatemost reliablytohumandosing.

kinetic advantages, combined with evidence of transporter-mediated limitationsandlocalmucosaleffects,provideamechanistic foundationfortheclinicalobservationsdiscussedlater,including studiesinallergicrhinitisandviralrespiratorydisease.

3.4Buccaladministration

Incontrasttotherapidnasalabsorption,buccaldelivery

4PharmacokineticsofCPMin animalmodels

Animalmodelsprovideessentialmechanisticcontextfor CPM pharmacokinetics, highlighting how differences in protein binding, hepaticmetabolism,mucosaltransport,andvascularphysiology influencesystemicexposure.Rodent,rabbit,canine,bovine,and provides a slower but more controlled mucosal uptake, equinestudiescollectivelyillustratethedegreetowhichspecies-

FIGURE3
Comparison of intranasal route bioavailability between dogs and humans.Simulatedcomparisonofbloodplasmaconcentrationsof chlorpheniareminemaleate(CPM)followingoralandintranasal administration.Concentration–timeprofilesweremodeled usingpublishedhumanpharmacokineticparameters(Tooretal., 2001;Kotzanetal.,1982;Vallneretal.,1982;Huangetal.,1982; Sanchez-Gonzalezetal.,2021;Sanchez-Gonzalezetal.,2022).The figurewasgeneratedbytheauthorsanddoesnotreproduceany previouslypublishedmaterial.

translatetohumansandhelpexplainthedrug'slongterminal half-life.

4.2Canineandbovinemodels

Incontrasttorodentsandrabbits,canineandbovinemodels havebeenespeciallyinformativeforevaluatingmucosaland intranasaldeliveryofCPM.Thesespeciesprovidedirectinsight intonasalvascularresponses,transporter-mediatedefflux,and mucosalpermeability,factorsthatarehighlyrelevanttomodern intranasalformulations.

Caninemodels,particularlyregardingnasaldelivery,have showndistinctiveresponsestoCPM(IchimuraandJackson, 1985).FoundthatCPMinducedintensevasoconstrictionin isolatedcaninenasalbloodvessels,whichdifferedsignificantly fromotherH1antihistamines(IchimuraandJackson,1985). (LungandWang,1987)reportedthatCPMcauseddifferential specificphysiologyshapesabsorptionandclearance,thereby informingthetranslationalrelevanceofnon-humanfindingsto

effectsonnasalvascularandairwayresistanceindogs,suggesting thatlocalizedvasculartonecouldimpactdrugabsorptionin intranasal formulations (Lung and Wang, 1987). Figure 3 comparesthebioavailabilityoftheintranasalroutebetweendogs andhumans(LungandWang,1987).

More recent data further confirm the rapid intranasal absorptionofCPMincanines.Inthenon-GLPsingle-dosestudy (Monaikul et al., 2023), two female Beagle dogs received 100 µL of a 70mg/mLchlorpheniraminemaleatesolutionpernostril(200µL total). Peak plasma concentrations were observed at 5 min (T_max = 0.083h)withmeanC_max≈472ng/mL(range295–650ng/mL) and $AUC_{0–8h}$ ≈345 ng h/mL. Plasma levels declined rapidly to ≈1% of C_max by 8 h, indicating fast mucosal uptake and short systemic persistenceinthismodel.Notreatment-relatedclinicalsignswere reported. These findings corroborate earlier canine vascular studies humandosing.

4.1Rodentsandrabbits

Rodentsandrabbitsoffertheclearestinsightinto CPM'sbasic

andquantitativelydemonstratethattheintranasalrouteachieves veryrapidsystemicexposurewhileremainingwell-tolerated. Together,theystrengthenthetranslationalrationalefornasal disposition mechanisms, including tissue distribution, hepatic CPMformulationsinhumans. extraction,andproteinbindingdynamics.Rodentsandrabbitshave Takentogether,caninedataemphasizethatCPM'sintranasal servedasessentialmodelstocharacterizethepharmacokineticsof absorption is rapid, concentration-dependent, and heavily

CPM.Figure2comparessingledosesbetweendifferentspecies. Ina landmarkstudy,HuangandChiou(1981)demonstratedrapid intravenousdistributionofCPMinrabbits,withhightissue-to-plasmaconcentrationratiosinlungs(160-fold),kidneys(80-fold), andbrain(31-fold)(HuangandChiou,1981).Thevolumeof distributionreached10.8L/kg,andthehepaticextractionratiowa s calculated at 0.88 (Lung and Wang, 1987). This high tissue affinity was attributedinparttorelativelylowplasmaproteinbindinginrabbits (44%),comparedtohumans(~70%).

influencedbylocalvascularandtransporteractivity.These mechanisticfeaturesobservedincanineandbovinenasalstudies rapidmucosaluptake,vascularresponsiveness,andtransporter-mediatedeffluxcloselyparallelthosedocumentedinhuman intranasalstudies,reinforcingtheirtranslationalrelevance.

4.3Equinemodels(Thoroughbredhorses)

These species have also been used to characterize demethylated metabolites and simulate dose-dependent kinetics. Oral administrationconfirmedasubstantialpresystemiceffect.Thes e animaldatahavehelpedpredicthumanbioavailabilityandinform

Equine pharmacokinetic studies extend the interspecies comparisonbyillustratinghowmetabolicrateandclearancecan toxicologyassessments,especiallyregardingtheCNSeffectsan d accumulationinrenalorhepaticdysfunctionmodels(Huangand

drasticallyshortenCPM'shalf-lifeinlargemammals.Inequine (Kurodaetal.,2013).Oralbioavailabilitywaslow(approximately Chiou, 1981). These characteristics make rodent and rabbit particularlyusefulforunderstandinghowphysicochemicalfactor and protein binding drive CPM distribution, findings that chlorpheniramine

pharmacology (Kuroda et al., 2013), evaluated d- inThoroughbredhorsesusingbothintravenousandoralroutes 38%), with peak concentrations achieved at 1 h and pharmacodynamicresponseevidentat2hpost-dose(Kuroda etal.,2013).

TABLE1Summaryofpharmacokinetic,bioavailability,andmechanisticstudiesofchlorpheniraminemaleateacrossspecies.

Lung	andWang(1987)	Human	n=12 B n	ioequivalencestudy (nonspecificformulat ions)	stereospecificvs. Oral ns)	l
Cho	ChouandDonovan Ratn (1997)			Mechanisticstudy(in	vitro,ratnasalmucosa, I.V.,Intr	anasal
Hua	Huangetal.(1982) Human		n=5 P	Kstudy(human,IV	vs.oral) I.V.,O	ral
Huang	andChiou(1981)	Rabbit	n=6 P	Kstudy(rabbit,I.V.,	tissuedistribution) I.V	36and48hafterdosing Bolusof3mg/kg injection
Ichim	IchimuraandJackson (1985)	N=	g 6 r	Mechanisticstudy(d o responses)	g,nasalvascular N/A	vascularbeds

Tmax=8.7h,Cmax=6.8–20.2ng/mL Stereospecificenantiomers(−)areless bioequivalentthanthose(+) CmaxandAUCvalueswerehigherfor(+)S-chlorpheniramine ((+)S-CPAM) compared to (−) R-chlorpheniramine((−)R-CPAM)(13.3vs. 6.8ng/mL and409 vs.222 ng/ml/h,respectively) whileClt/Fand Vd/Fwerelower(9.8vs.17.61/h and 321 vs. 627 1, respectively). No difference was observedforTmaxandt½

There were no measurable concentrations of CPM intheCSFfollowingeitherintraarterialor intranasaladministration—nobioavailabilityof intranasalCPMintheCSF.

The average peak time after single oral dosing was 2.8hwithanaveragepeaklevelof17.9ng/mL half-livesobtainedinthisstudy(20.6–43.4h)

The harmonic mean of the half-life in six rabbits. (A-F)was2.57hwitharangeofL72–4.87h. Thesevaluesaresimilartothose(mean1.7h). Foundindogs,butweremuchshorterthan reported for humans 28 h from Peets et al., 115.6 h fromThompsonandLeffert,and22.5hfrom Huang et al—most extensive distribution in lungs, Brain, and Spleen. The lower percentage of serum protein binding in rabbits, as compared to those of dogs and humans (44% vs. 70% and 73%), might havecontributedinparttothelargervolumeof distributioninrabbits(Vareaof15.5L/kgvs. 5.25and3.36L/kg)

Chlorpheniraminemaleateandpyrilamine maleate caused the maximal contraction at a dose of6×10·3M.Chlorpheniramineinducedthe mostsignificantabsoluteresponse.CPM antihistamine does not need extracellular calcium ionstoinducecontractioninthistissue. Histamine does need extracellular calcium ions to causecontraction.Antihistaminesmayevoke direct contraction of blood vessels by depolarizing smoothmusclecellmembranescoupledwitha releaseofinternallyboundcalciumions

TABLE1(Continued)Summaryofpharmacokinetic,bioavailability,andmechanisticstudiesofchlorpheniraminemaleateacrossspecies.

Kan	Kandimalla and Donovan (2005)	Cow N=notspecified	MechanisticStudy(invitro,bovinenasal mucosa,transporterassay)	al	N/A	chlorcyclizine
	Kimetal.(2020)	Dog N=15	Bioavailabilitystudy(dog,oral,jellyvs. tablet formulation)	tablet Oral		mixed
K	Kotzanetal.(1982)	Humann=15	Bioavailabilitystudy(human,regularvs. controlled-release)	s. Oral		
	Kurodaetal.(2013)	Horsesn=4	PK/PDstudy(horse,IVandoral)		I.V.,Oral	500mLofwater

The submucosal to mucosal fluxes (Js–m) of CPM acrosstheolfactorymucosaweresignificantly greaterthanthemucosaltosubmucosalfluxes (Jm–s).Moreover,thesubmucosal–mucosal permeability of CPM was temperature dependent andsaturable.TheseresultsindicatethatCPMis effluxedfromtheolfactorymucosabyefflux transporterssuchasP-gpandMRP1.Transport studiesacrossinertpolymericmembranes demonstratedthatthepermeabilityofCPM decreasedatdonorconcentrationshigherthan 3 mM, suggesting that physicochemical properties suchasself-aggregationalsoplayaroleinthe reducedolfactorymucosalpermeabilityofthese compoundsathigherconcentrations

TheabsorptionofCPMwasmoredelayedand decreased by Tablet-H than by AAP. According to severalreports,CPM'sabsorptionrateisslow, probablybecausetheabsorptionoftheweakly basicdrug,CPM,occursmainlyinthesmall intestineandishardlyabsorbedinthestomach. According to the FDA's criteria, the syrup, jellies, andtabletswerenotbioequivalent.Evenso,the jelliesandsyrupshowedsimilarabsorptionrates andextents.Ontheotherhand,thetablets significantlydelayedandreducedtheabsorptio n ofthecoldmedicinescomparedtothesyrup

TheAUCofthecontrolledreleaseformu-lations wasnotequivalenttotheexactamountsofnon-controlled release products, nor were they equal to twotimestheAUCofthe4-mgsyrup,realizing thedifficultiesinvolvedinobtaininganexactA UC.Thecontrolled-releaseproductsalso extendedthetimenecessarytoattainpeakdrug levelscomparedtothe4-and8-mg

Theparametersestimatedfromthe pharmacokinetic/pharmacodynamiclinkmode l, Emax,EC50,andh,were79.2% ±12.1%,53.2±16.1ng/mL,and0.88±0.42,resp ectively.The effectof0.1mg/kgIVand0.5mg/kgP.O.doses wasverylow;therefore,theywerenotappliedto thepharmacokinetic/pharmacodynamiclink model.VerypoorbioavailabilityoforalCPMin Horises'lowbioavailability(approximately38%) indicates that a P.O. dose of 2.6 times the IV dose maybenecessary

TABLE1(Continued)Summaryofpharmacokinetic,bioavailability,andmechanisticstudiesofchlorpheniraminemaleateacrossspecies.

MoMonaikuletal.(2023)	Beagledog(n=2, female)	Non-GLPpharmacokineticstudy	cstudy I	Intranasal	200µLtotaldose)
LunLungandWang(1987)	Dogn=9 na	Mechanistic study (dog,	sal airway resistance) I	Intranasal	
SSekharetal.(2008)	Humann=8	PK/Buccal delivery study (h buccalpatches)	uman, mucoadhesive O	Oral,Buccal	usingHPLC.
VVallneretal.(1982)	Humann=15	PK/PDstudy(human,mu	ltipleoraldosing)	Oral	aafterthat
((Tooretal.,2001)	Humann=15	PK/Bioavailabilitystudy(h oral)	uman,intranasalvs. Oral,Intr	anasal	

Afterintranasaldosing,rapidabsorptionwas observed with Tmax = 5 min (0.083 h) and mean Cmax=472.5ng/mL(range295–650).Mean $AUC_{0–8}$ = 344.5 ng h/mL. Plasma concentrations declined to ~1% of Cmax by 8 h, indicating rapid clearance. No clinical adverse signs were reported. Studysupportsfastsystemicexposureandgood tolerabilityfollowingnasaladministration

Atdosesof<1mg,CPMincreasesvascular resistanceanddecreasesairwayresistance.A dose>1 mg, CPM decreases vascular resistance. In dosesoflessthan1mg,increasednasalvascular resistancebutdecreasednasalairwayresistance , suggestingaconstrictoractiononthearterioles and a decrease in vascular capacitance by opening arteriovenousanastomosesordilatationofthe musculavenules.However,whendoseshigher than1mgweregiven,nasalvascularresistance decreasedsignificantly,whilenasalairway resistancedecreasedonlyslightly.Thissuggests that the drug in high doses causes dilatation of the arteriolesbuthasanegligibleeffectonthe capacitancevessels

Theresultsofthebuccalabsorptionstudy (Figure2)revealedthatCPMcouldbeabsorbed throughtheoralmucosalmembranes.Wefound that ~45.90% of the drug was absorbed in 16 min. The drug was absorbed at a rapid rate for the first 4 min, after which the drug absorption continued at a uniform rate. The volunteers did not swallow thesolution.Thiswasevidentfromthe observationthatthetotalquantityofphenolred (392.40±5.31µg)

Thedisappearancecurvesofthethreeproducts areessentiallyparallel,indicatingsimilarhalf-lives.Thehalf-livescalculatedfromthesecurves are 24·5 h for the repeat action tablets, 25·4 h for thebarriercoated-beadcapsules,and25·1hfor theconventionalreleasetablets

Nasallyappliedchlorphenaminemaleatewas readilyabsorbed,reachingpeakplasmalevels mainly between0.25 and 3.0 h after ap-plication. The initial steep increase in plasma drug levels was followedbyagradualdecreaseovertimeupto 24hafterdosing,andwasassociatedwith secondaryandtertiarypeaks

TABLE2Interspeciescomparisonofpharmacokineticparametersof Chlorpheniramineindifferentadministrationroutes.

Species	Route	Cmax (ng/mL)	Tmax (h)	AUC(ng-h/mL)orF(%)	$T_{1/2}$(h)	Keynotes
Human	Oral(IRtablet,4mg)	5.73±1.08	2.17 ± 0.41	57.85±15.50	NR	Single-dose,healthyvolunteers
	Oral(steady-state; conventional&CR products)	25.9–32.5	3.9–8.4	837–1,202	24.5–25.4	Multiple-dose,day-7steady-stateacrossproducts; rangesextractedfromtables
	Intranasal(0.4%)	NR	0.25–3.0	NR	NR	Healthymales(n=24);peakwindowreported
	Buccal(mucoadhesive patch,4mg)	6.16±0.99	3.33 ± 0.82	84.99±17.96	NR	Single-dose,healthyvolunteers
	Intravenous(5mgbolus)	N/A	0(IV)	NR	22–23	Twosubjects;terminalhalf-livesreportedin summary
Horse	Oral(0.5mg/kgd-CPM)	65.0±12.3	1.20 ± 0.45	273±82.8	2.12±0.71	n=5;d-isomeronly;one-compartmentPOmodel
Rabbits	Intravenous (0.5–3mg/kg)	N/A	0(IV)	NR	2.57(range 1.72–4.87)	Harmonicmeant½acrosssixNZWrabbits
Dog	Intranasal(singledose, 0.4%CPMspray)	472.5±250 (range 295–650)	0.083 (5min)	344.5±73.0	~1.6–1.7	Two female Beagle dogs received a single 200 µL total dose(100µLpernostril)of70mg/mL chlorpheniraminemaleatesolution.Rapid absorptionobservedwithpeaklevelsat5min and >99% decline by 8 h. No adverse events reported
	Intravenous	NR	NR	NR	1.7h (elimination)	Distributiont½α12.5min;Vdβ525%BW;F_Oral: upto39.4%dependingondose
	Oral(50–200mg)	NR	NR	F=9.4–39.4%	NR	Absolute bioavailability varied with dose (50–200 mg solutions)
Rat	Intranasal	NR	NR	NR	NR	TissuedistributionstudiesonlynosystemicCmax, Tmax,orAUCreported
	Intravenous(Racemate)	NR	NR	HigherAUCfor (+)-Senantiomer	18.2min((−)); 50min(+)	Stereoselective PK after IV; clearance differences and proteinbindingnoted
	Oral/IV(20mg/kg racemate)	NR	NR	HigherAUCfor (+)-Senantiomer	NR	Stereoselectiveabsorption/metabolisminrats
Cow	Exvivonasal	NR	NR	NR	NR	Distributionstudiesinbovinenasalmucosa:drug retentionbutnosystemicPKreported

TheIVformulationshowedrapidclearanceandashorthalf-life(~2.7h),furtherreinforcinginterspeciesdifferences.Thelow oral bioavailability suggests that substantially higher doses may be neededinequinemedicinecomparedtootherspecies.These

5Comparativebioavailabilityand bioequivalencestudies

Beyondspeciesdifferences,formulation-dependentbehavior markedlyinfluencesCPMexposure.Understandingtheinterplay betweendosageformandpharmacokineticsisessentialwhen comparing dataacrossroutesandspecies. Theimpactof formulation on CPM's pharmacokinetics has been well-documented(Kotzanetal.,1982).and(Vallneretal.,1982) demonstratedthatcontrolled-releaseformulationsextendedthe

findings emphasize the importance of species-specific pharmacokinetics when translating dosing regimens from preclinicalmodelstoveterinaryorhumansettings(Kuroda etal.,2013).Thisrapidclearancecontrastssharplywiththe prolongedhalf-lifeinhumans,reinforcingthatextrapolation across species must account for differences in hepatic metabolism,bodysize,andproteinbindingcapacity.

Together,theanimaldataillustratehowspecies-specific differencesinclearance,proteinbinding,andmucosalabsorption

timetopeakconcentrationbutdidnotyieldbioequivalencein productsoftenproducedincompleteabsorption,andtheirAUC shap pharmacokinetic behavior. These findings provide a mechanisti backdrop for understanding why certain CPM formulationsperforminconsistentlyacrossstudies.Buildingon theseinsights,thefollowingsectionevaluateshowformulation AUCcomparedtoconventionalforms.Infact,controlled-release values were not dose-proportional to the regular- counterparts(Kotzanetal.,1982;Huangetal.,1982).

Buietal.(2000)addedanotherlayerbystudyingthe stereospecificbioavailabilityofracemicCPM.Theyobserved desig influences CPM bioavailability in both human and preclinicalsystems. significantdifferencesinsystemicexposurebetweenenantiomer with (+)-CPM showing higher Cmax and AUC compared to the (−)

enantiomer(Hiepetal.,2000).Thesefindingsindicatethatboth formulationandstereochemistryaffectCPM'spharmacokinetic s.
Recentcomparisonsbetweenjellies,syrups,andtabletsindogs confirmedthatjelliesandsyrupshadcomparableabsorption.In contrast,tabletsdelayedabsorptionandreducedthemaximum concentration(Cmax),possiblyduetoprolongeddisintegration andpH-dependentsolubility(Kimetal.,2020).Thesefindings reinforcetheregulatoryandbiopharmaceuticalchallengesin developingconsistentandinterchangeabledosageforms.Table 1 summarizesthereviewedstudies.

desmethylcompounds. The t½ isincreasedin thepresence ofrenal dysfunction, whereas it is decreased in children (Rumore, 1984). The exact mechanism of presystemic first-pass elimination and the effects ofdoselevelsonthisprocessarecurrentlyunclear.Ithasbeen reportedthatCPMispredominantlymetabolizedbycytochrome P4502D6(CYP2D6)(Huangetal.,1982).Biopharmaceuticaland pharmacokineticstudiesinhumansaftersingleormultipledoses revealwideinterindividualpharmacokineticvariations.

The usual recommended oral dose for adults is 4 mg q4-6 h, or 8–12 mg in the form of sustained-release tablets two to three times

Thes clinical findings align with the pharmacokinetic daily. The recommended oral dose for children aged six to

propertiesofintranasalCPM,particularlyitsrapidabsorption (Tmax0.25–3h),highearlylocalconcentrations,andpartial first-pass bypass.ThesePKattributesareconsistentwiththe therapeuticgoalsforearly-stageviralinfections,whererapid

2mgq4-6hand1mgq4-6hforchildrenagedtwotofive. Intravenous,intramuscular,orsubcutaneousinjectiondosesof 5–40mghavealsobeenreported(Rumore,1984).Understanding CPMdispositioninanimalmodelsisessentialforinterpretingits mucosa action and dense nasopharyngeal exposure may mechanistic behavior and translational applicability.

meaningfullyinfluenceviralreplicationdynamics.

6Discussion

Thisdiscussionintegrateshumanandanimalpharmacokinetic findings, formulation-dependent variability, and mechanistic insights tohighlighthowCPM'sabsorption,distribution,andclearance patternsshapeitsclinicalapplications.Bysynthesizingroute-

differences in metabolism, protein binding, mucosal transport, and vascular physiology provide a foundation for explaining why certain routes,especiallyintranasaldelivery,behavedifferentlyinhumans thaninpreclinicalsystems.

Animal studies revealed distinct pharmacokinetics. Interspecies differencesaremostly related totheability to metabolizethedrug, which seems to be elevated in horses (Kuroda et al., 2013). In horses, oraladministrationofd-CPM(0.5mg/kg)producedaCmaxof 65.0 ng/mL at 1.2 h with an AUC of 273 ng h/mL and a t½ of 2.1 h (Kurodaetal.,2013).Inrabbits,IVadministrationyieldeda half-lifeof2.6h(HuangandChiou,1981).Rats exhibitedstereoselectivePK,withthe(+)-Senantiomershowing prolongedhalf-life(50min)comparedwiththe(−)-Renantiomer (18.2min)(Sakuraietal.,1992;Tungetal.,2001). 4mgdose,withanAUCof57.9ngh/mL(Vallneretal.,1982). Controlled-releaseandmultiple-dosestudiesreachedsteady-state

specific characteristics with interspecies data, this section contextualizes CPM's therapeutic potential particularly for intranasal and transmucosal delivery and identifies the translationalimplicationsformodernclinicaluse.

Across studies, CPM demonstrated highly variable pharmacokineticsdependingonspecies,formulation,androute of administration(Table2).Inhumans,oralimmediate-release formulationsshowedaCmaxof5.7ng/mLat2.2hafterasingle

Indogs,intranasaldeliverysignificantlyalterednasalvascular resistance and blood flow, consistent with rapid systemic absorption (IchimuraandJackson,1985;LungandWang,1987).Inabovine model,theintranasalrouteexhibitsdose-andpH-dependent limitations,assaturationdynamics(maximalpermeabilityof Cmaxof25.9–32.5ng/mLwithextendedTmaxof3.9–8.4hand 15–25 cm/s) impede permeability at drug concentratio

AUC837–1,202ngh/mL(Hiepetal.,2000;Kotzanetal.,1982; Vallner et al., 1982; Huang et al., 1982). Buccal mucoadhesive delivery

exceeding3nMandanoptimalpHof6.2(Kandimallaand Donovan,2005).Incattle,exvivonasalstudiesdemonstrated
(4 mg) achieved Cmax of 6.2 ng/mL at 3.3 h with AUC 85.0 measurable distribution and receptor-mediated effect

(Sekhar et al., 2008). Intranasal CPM (0.4%) in healthy males reached peak plasma concentrations between 0.25 and 3.0 h (Toor et al., 2001). Intravenous bolus dosing (5 mg) yielded a terminal half-life of 22–23 h (Huang et al., 1982). In practical terms, these parameters indicate that CPMexposureishighlydependentonbothformulationand absorptionsite,whichmustbeconsideredwheninterpreting clinicaleffectivenessacrossdeliveryroutes.

(KandimallaandDonovan,2005).

Clinical studies of intranasal CPM in COVID-19 demonstrated efficacyinearlysymptomaticrelief.Arandomizedcontrolledtrial reported reduced symptom scores and viral clearance compared to placebo(Sanchez-Gonzalezetal.,2021).Observationalstudies confirmedclinicalimprovementinlargerpatientcohorts(Ferrer etal.,2025),andapooledanalysishighlightedpotentialbenefitin reducingpost-acutesequelae("longCOVID")(Valerio-Pascua etal.,2024).

Taken together, these data underline three consistent pharmacokineticthemes:(i)CPMdisplaysrapidabsorptionwith markedformulationdependence;(ii)alongeliminationhalf-life supports less frequent dosing than traditionally prescribed; and (iii) extensivetissuedistributionandhighproteinbindingprolong systemicexposure.Thesefeaturesprovideamechanisticbasisf or thevariabilityobservedacrossstudiesandguidetheinterpretatio n ofintranasalandbuccaldelivery,wherepartialavoidanceoffirst-passmetabolismandhighmucosalvascularityalterbothonset

6.1Interspeciesvariabilityin pharmacokinetics

Thecomparativeanalysisrevealedstrikingdifferencesinhalf-life across species. Rabbits displayed rapid elimination (t½ ~2.6 h), while humans consistently showed prolonged persistence andexposure.

With a serum half-life (t½) of ~20 h in adults, CPM's linewithearlierreportsofstrongproteinbindingandslow fromthebodyisprimarilybymetabolismtomonodesmethyland clearance Dogs and horses exhibited intermediate value s, .

underscoringtheroleofspecies-specificphysiology,including proteinbindingcapacityandhepaticmetabolism,inshaping CPMdisposition.Thesedifferenceslimitthedirectextrapolation ofpreclinicaldatatohumansbutprovidemechanisticinsightinto thedeterminantsofCPMpharmacokinetics.

6.2MechanisticinsightsfromanimalandIn vitrostudies

EffluxtransportersrepresentakeylimitationtoCPM's effectiveness,particularlyinnasalandCNSdelivery(Kandimalla and Donovan, 2005). Confirmed that CPM is transported out of the nasal mucosa by P-gp and MRP1, reducing its brain availability. This

requiringq6hadministration.ThisPKprofile,togetherwiththe practicalobjectiveofday–nightsymptomcontrolandtherapid onset afforded bythe intranasalroute, supported theselection of a twice-dailyregimeninourchallenge-studyschedule(Day0–5), aligningclinicaloperationswiththedrug'slongterminalhalf-life andensuringadequateexposureover24-hcycles.

6.4TranslationallinkbetweenPKand clinicalapplications

Thecombinedpharmacokineticevidenceacrossspeciesand administrationroutesclarifieswhyCPMperformsdifferentlyin specificclinicalscenarios.Thelongeliminationhalf-lifeand activetransportwasenergy-dependent,temperature- extensiv tissue distribution observed in humans suppor

inhibitedbyverapamilandquinidine,confirmingtransporter specificity(KandimallaandDonovan,2005).

In addition to transporter effects, CPM shows moderate protein binding (~70%) and wide tissue distribution (Ichimura and Jackson, 1985). Demonstrated that CPM's action on nasal vasculature might involve direct smooth muscle activation independent of extracellular

infrequentdosingandsustainedreceptoroccupancy,whereasthe rapid absorption and early peak concentrations following intranasal delivery make this route particularly suited for acute symptom relief andpotentialantiviralaction.Thesekineticdistinctionsprovidea mechanisticfoundationformatchingCPM'spharmacokinetic propertiestotherapeuticobjectives.

calcium,suggesting analternate vasoconstrictivemechanism Preclinical data also contextualize clinical observations.

(IchimuraandJackson,1985).Sucheffectscouldaltermucosal bloodflowandmodulatedrugabsorptiondynamics(Ichimura

and bovine nasal studies demonstrate that mucosal vascularity, local vasoconstriction,andtransporter-mediatedeffluxsignificantly
andJackson,1985).

These insights underscore the necessity of considering both drug

influenceCPMuptake.Thesemechanisticfeaturesalignclosely formulationandmucosalphysiologyindesigningnasaland transmucosalsystems.Carriersystemsortransporterinhibitors

withfindingsfromhumanintranasalstudies,whichshowfast absorption,limitedcentralnervoussystempenetration,andhigh early mucosal exposure factors relevant in conditions such as allergic rhinitisandearlyviralinfection.

may significantly improve CPM bioavailability in future

formulations(Rizvietal.,2024;KandimallaandDonovan,2005). Mechanistically, these observations suggest that CPM is governed by abalancebetweenrapidmucosaluptakeandactiveefflux constraints,resultinginhighearlyconcentrationsbutlimited sustainednasalretention.Thisinterplayexplainstherapidonset seen in intranasal human studies and provides a rationale for novel formulationstrategiesaimedatenhancingresidencetimeor transientlymodulatingefluxactivity.

6.3Considerationfordosingfrequency

GiventhatChlorpheniramineinadultsexhibitedaterminal eliminationhalf-lifeconsistentlyinthe~20–25hrangeacross

Taken together, the integration of PK behavior and mechanistic dataestablishesacoherenttranslationalframework.This synthesis supports ongoing efforts to design optimized intranasal, buccal, and modified-releaseformulationswhileinformingdoseselection, therapeutictiming,andfutureclinicalstudydesigns.

6.5Clinicalimplications

Human studies have consistently shown the prolonged half-life and systemic persistence of CPM, supporting its efficacy as a long-actingantihistamine.However,variabilityinabsorptionhighlights theimportanceofformulationdesign.Buccalandintranasal administrationappearpromisingforrapidsymptomreliefin intravenousandmultiple-doseoralstudies(Kotzanetal.,1982; allergic conditions, while oral controlled- product Vallneretal.,1982;Huangetal.,1982),a12-hdosingintervalis demonstrate inconsistent systemic exposure. The favorabl

pharmacokineticallycoherentandavoidsunnecessaryre-dosingat 6-hintervals.InthehumanPKliteraturesynthesizedinour manuscript,theparallelterminalslopesafterrepeatedoral administrationyieldedhalf-lives≈of25h,andintravenous

tolerabilityprofileobservedacrosshumanstudies,coupledwith continued clinical use of CPM, while also emphasizing the need for careful dose selection.Thesefindingscollectivelyhighlighthow CPM'sroute-specific pharmacokinetic behavior can be leveraged to objectivesrapidmucosalactionforviralorallergicindications

dose-dependent vascular effects in animals, supports the

studies similarly reported terminal half-lives of ~22–23 h (Vallne et al., 1982; Huang et al., 1982); intranasal

administrationachievedrapidabsorption(Tmax≈0.25–3h)with systemicexposurecomparabletooraldosing(Tooretal.,2001; Sanchez-Gonzalezetal.,2021;Sanchez-Gonzalezetal.,2022).

Under these conditions, with k = ln2/t_1/2 ≈0.028–0.035 h^{-1}, the expectedsteady-statefluctuationacrossa12-hintervalremains modest(Cmax,ss/C_min,ss≈e^{kτ}≈1.3–1.5),indicating sustainedH1-receptorcoverageovereachdosingintervalwithout

versussystemicpersistenceforchronicinflammatoryconditions.

6.6Futureperspectiveandchallenges

Despiteitslonghistoryofclinicaluse,substantialknowledge gaps remain in the pharmacokinetics of CPM, particularly regarding

moderndeliverysystems.Pharmacokineticcharacterizationof contemporaryformulationssuchasnasalsprays,bioadhesive gels, and buccal films has largely been limited to small, pharmacokinetic and heterogeneousstudies,oftenwithinconsistentendpointsand non- sampling schedules. As a result, the comparativeperformanceoftheseformulationsremainsdifficult to interpret, and optimaldosing strategiesareyet to be established (Rizvietal.,2024;Torresetal.,2021;Kimetal.,2020).

scale, applications in infectious disease. Further large- well-designedclinicaltrialsarewarrantedtoconfirmthesepromising results and to establish standardized

pharmacodynamicprofilesacrossdiversepopulations.

Authorcontributions

Another key challenge is the significant interindividual variability observe in CPM exposure. Polymorphisms in CYP2D6,whichplaysacentralroleinCPMmetabolism,along withage-relatedphysiologicalchanges,renaldysfunction,and comorbidconditions,mayprofoundlyinfluencedrugdisposition.

CA-P: Conceptualization, Formal Analysis, Methodology Resources,Supervision,Validation,Writing–originaldraft,

Writing–reviewandediting.DP-V:Datacuration,Investigation, Validation,Writing–originaldraft,Writing–reviewandediting. KG-Z:Datacuration,Investigation,Validation,Writing–original

Thes factors warrant systematic evaluation, particularly in draft,Writing–reviewandediting.GF:Conceptualization,

populationsmostlikelytobenefitfromnon-oraldeliveryroutes, including pediatric, geriatric, and respiratory-compromised patients (Rizvietal.,2024;LungandWang,1987).

Investigation,Methodology,Projectadministration,Resources, Supervision, Validation, Visualization, Writing – review and editing.

Several translational questions also require clarification. AlthoughintranasalCPMhasshownencouragingresultsin allergic rhinitis an early COVID- treatment, critical paramete such as dose– relationship therapeutic timing,andcomparativeeffectivenessversusexistingstandard-of-caretherapiesremainundefined.Addressingthesegapswillbe essentialfordeterminingthetrueclinicalvalueofCPMinboth allergicandantiviralapplications(Rizvietal.,2024;Torres etal.,2021).

Looking ahead, future research should emphasize stereospecific

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Populationpharmacokineticmodelingmayfurtherhelprefine dosingrecommendationsandimproveindividualizedtherapy.

7Conclusion

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Theauthor(s)declaredthatgenerativeAIwasnotusedinthe

The pharmacokinetics and pharmacodynamics of chlorpheniramine maleate (CPM) demonstrate marked interspeciesandformulation-dependentvariability.Preclinical studiesinrabbits,horses,dogs,cows,andratsconsistently highlightdifferencesinab-sorptionrates,bioavailability,and half-lifeacrossspecies.Thesefindingsunderscorethechallenges of extrapolating animal data directly to humans and emphasize the needforstereospecificevaluationofCPM.

Inhumans,oralandbuccalformulationsachievemodest systemicexposurewithvariablebioavailability,whereasintranas al deliveryemergesasthemostpromisingroute,achievingrapid mucosalabsorptionandfavorableclinicaloutcomes.Recenttrial s of intranasal CPM in COVID-19 demonstrated improved symptom

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control and viral clearance, with complementary observational pooledevidencesuggestingbenefitsinmitigatinglongCOVID.

Takentogether,thesefindingspositionintranasalCPMasa candidate for early therapeutic intervention in respiratory illnesses, bridgingitshistoricalantihistaminerolewithpotentialnew

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