REVIEW ARTICLE

Active pharmaceutical ingredients available as substances for extemporaneous preparation in veterinary medicine in the Czech Republic

Účinné látky dostupné jako substance pro magistraliter přípravu ve veterinární medicíně v České republice

Zbyněk Sklenář • Kateřina Horáčková • Hana Bakhouche

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Summary

In veterinary medicine, extemporaneously prepared drugs can be also used in therapy. In the recent four years the selection of suitable compounds for extemporaneous (magistral) preparation has been expanded and new possibilities for the creation of formulas have appeared. The paper reports on the substances available for compounding that can be used in veterinary medicine, in the pharmacotherapeutic classes antibiotics, antimycotics, antiseptics, corticosteroids, emollients and epithelizing agents, anti-inflammatory drugs, local anesthetics, decongestives, beta-blockers and calcium channel blockers, antiemetics and prokinetics, sedatives and hypnotics. The emphasis has been placed on newly available substances. Examples of suitable magistral formulas are presented that can replace mass-produced drug products which are not readily obtainable. The aim of the paper is to inform pharmacists and veterinarians about new possibilities of drug compounding.

Keywords: compounded preparations • extemporaneous preparation • compounding of drugs possibilities • magistral formulas in veterinary medicine

Souhrn

Také ve veterinární medicíně stále nacházejí v terapii uplatnění připravované léčivé přípravky. Protože došlo během posledních 4 let k významnému rozšíření nabídky vhodných substancí pro magistraliter přípravu, objevily se tak i nové možnosti při vytváření receptur. Příspěvek podává přehled o léčivých látkách dostupných pro individuální přípravu, které nacházejí uplatnění ve veterinární medicíně, v žádaných farmakoterapeutických skupinách léčiv – antibiotika, antimykotika, antiseptika, kortikosteroidy, emoliencia a epitelizancia, antiflogistika, lokální anestetika, dekongestiva, betablokátory a blokátory vápníkových kanálů, antiemetika a prokinetika, sedativa a hypnotika. Důraz je kladen na substance nově dostupné. Prezentovány jsou i příklady vhodných receptur, které mohou nahradit obtížně dostupný přípravek komerčně vyráběný. Cílem příspěvku je informovat farmaceuty a veterinární lékaře o případných nových možnostech magistraliter přípravy léčiv.

Klíčová slova: magistraliter přípravky • individuální příprava • možnosti individuální přípravy léčiv • receptury magistraliter ve veterinární medicíně

Introduction

Compounded drugs (magistral preparations) take an important place in human and veterinary medicine. Since 2010 a significant increase of newly available compounds for extemporaneous preparation in pharmacies has occurred, so the possibilities of compounding have been extended and the importance of individual (magistral) preparation has been bolstered. It is possible to prepare requested dosage forms or specific formulations (including combinations of different ingredients) that are not available as registered products. The most important

PharmDr. Zbyněk Sklenář, Ph.D., MBA (✉) • H. Bakhouche
Institute of Pharmacology
First Faculty of Medicine, Charles University in Prague
Albertov 4, 128 00 Prague 2, Czech Republic
e-mail: zbynek.sklenar@gmail.com

K. Horáčková
Department of Analytical Chemistry, Faculty of Pharmacy in Hradec Králové, Charles University in Prague, Czech Republic

substances available for compounding are presented in the paper in selected pharmacotherapeutic groups that can be used in veterinary medicine, including possible compounded formulas that can be prepared in pharmacies. The veterinarians thus gains the possibility to acquaint themselves with this news.

Most frequently, medicines for topical (e.g. skin, ear, nasal, ocular), oral (solutions, gels, viscous suspensions) and oromucosal (slimes, gels, solutions, suspensions) application have been prepared. As dosage forms, hydrophilic and oleophilic ointments, creams, pastes, gels, solutions, liquid suspensions and emulsions, rectal and vaginal divided formulations, eye, ear and nasal drops, sprays, oral solutions, gels, capsules, oromucosal solutions, suspensions and mucoadhesive pastes have been used.

Selected pharmacotherapeutic groups

Antibiotics

Antibiotics in compounded drugs particularly used for local application (skin, ear, intraoral etc.) are **neomycin sulphate** *(Neomycini sulfas)*, **chloramphenicol** *(Chloramphenicolum)*, **tetracycline hydrochloride** *(Tetracyclini hydrochloridum)*, **erythromycin** *(Erythromycinum)*, **metronidazol** *(Metronidazolum)*, and **gentamicin sulphate** *(Gentamicini sulfas)*. Other compounds such as chloroxine *(Cloroxinum)* and nitrofurantoin *(Nitrofurantoinum)* are not used in veterinary medicine.

Formulas No. 1 and No. 2 are examples of combined preparations: an antibiotic, a corticosteroid and an antimycotic or an antibiotic and a corticosteroid that can be used for *otitis externa* therapy.

Formula No. 1: Ear combined drops

Clotrimazolum	0.5
Chloramphenicolum	1.0
Dexamethasoni acetas	0.01
Propylenglycolum	
Ethanolum 60%	aa ad 50.0

The following formulation can be a substitute for the commercial product (ear drops), registered and available in the past.

Formula No. 2: Ear drops with chloramphenicol and triamcinolone

Chloramphenicolum	1.0
Triamcinoloni acetonidum	0.05
Propylenglycolum	ad 10.0

Antiseptics

Chlorhexidine has been used widely as a biguanide antiseptic. In marked products, chlorhexidine hydrochloride has been used; for compounding, chlorhexidine digluconate has been obtainable as a solution with a content of 20% (m/V) of chlorhexidine digluconate *(Chlorhexidini digluconatis solutio)*. It has been incorporated into solutions or gels. **Cetrimide** *(Cetrimidum)* and **carbethopendecinium bromide** *(Carbethopendecinii bromidum)* are representatives of the quaternary ammonium bases antiseptic group. **Iodine** *(Iodum)* and **povidon iodine** *(Povidonum iodinatum)* belong to the group of halogen- releasing agents. Povidon iodine is preferred in therapy. There are standardized formulas containing povidon iodine obtainable abroad, e.g. Iodpovidon-Glucose-Salbe[1]. **Hydrogen peroxide** *(Hydrogenii peroxidum)* as an atomic oxygen-releasing agent has been used constantly, but to a limited extent, in concentration of 3%, and **potassium permanganate** *(Kalii permanganas)* as a lightly pink solution for rinsing. The group of phenolic compounds includes **phenol** *(Phenolum)* as a component of Castellani solution *(Solutio Castellani)* or in combination with camphor and ethanol as Chlumský solution *(Solutio phenoli camphorata)*, that has been used separately e.g. for wound tamponade, or has been incorporated into an anti-inflammatory ointment. **Resorcin** *(Resorcinolum)* and **thymol** *(Thymolum)* are other phenolic compounds, used rarely. Certain importance have some organic colouring agents (organic colors), although their therapeutic sense has been frequently overestimated. **Brilliant green** *(Viride nitens)* or **methylrosanilinium chloride** *(Methylrosanilinii chloridum)*, used in aqueous or aqueous-alcoholic solutions intended for the skin or mucosa, belong to this group. For fish, **acriflavine** *(Acriflavini chloridum*, syn. trypaflavine) has been used.

Other antiseptics have been used rarely, e.g. from the group of heavy metals compounds only **silver nitrate** *(Argenti nitras)* has been used.

When combining antiseptics, caution is necessary. Antiseptics can show numerous interactions when combined with other drugs, e.g. chlorhexidine with nystatin – unsoluble salt arises and the effect on *Candida albicans* decreases significantly[2]. Chlorhexidine combined with cetrimide is especially toxic in dogs and cats[3].

Antimycotics

Until recently just non-specific antimycotics were accessible for compounding, e.g. benzoic acid, salicylic acid or undecylenic acid, phenol, iodine, colouring organic agents. **Clotrimazole** *(Clotrimazolum),* **nystatin** *(Nystatinum)* and **miconazole** *(Miconazolum)* are newly available for compounding thereby a wider spectrum of preparations with local antimycotic effect can be compounded. Clotrimazole can be used for local therapy of ocular, nasal and ear mycosis.

Miconazole is suitable for oromucosal, oral administration and dermal administration. The suitable formulations have been still in development.

Formula No. 3: Clotrimazol eye drops, solution

Clotrimazolum	0.1
Helianthi oleum raffinatum	ad 10.0

Nystatin can be incorporated into topical skin, ear, oromucosal and oral formulations. If a galenic form of paste is required, extemporaneous preparation would be used, e.g. with an addition of alpha tocopherol acetate as the epithelizing agent. In the cases of miscellaneous bacterial and mycotic infections, neomycine sulphate can be incorporated into the paste.

Formula No. 4: Nystatin paste with vitamin E (and neomycin)

Nystatinum (6660 IU/mg)	0.3
(Neomycini sulfas (660 IU/mg)	0.1)
Tocoferoli alfa acetas	0.4

Olivae oleum raffinatum	2.0
Zinci oxidi pasta	ad 20.0

Corticosteroids

To this group belong the previously available **dexamethasone**, in alcoholic form *(Dexamethasonum)* and ester *(Dexamethasoni acetas)*, **hydrocortisone**, both its alcoholic form *(Hydrocortisonum)* and ester *(Hydrocortisoni acetas)*, **prednisolone** *(Prednisolonum)*, **prednisone** *(Prednisonum)*, **betamethasone dipropionate** *(Betamethasoni dipropionas)*, **fluocinolone acetonide** *(Fluocinoloni acetonidum)* and **triamcinolone acetonide** *(Triamcinoloni acetonidum)*. They can be incorporated into topical preparations for external use (solutions, ointments, creams, pastes), some of them can be used for compounding of mucoadhesive pastes for use in the mouth cavity – the paste has an adhesive effect for a certain time on the moist mouth mucosa.

Formula No. 5: Mucoadhesive paste with triamcinolone

Triamcinoloni acetonidum	0.02
Hypromellosum (app. v. 17350)	8.0
Vaselinum album	4.0
Paraffinum liquidum	ad 20.0

Emollients and epithelizing agents

Emollients have been used for skin softening, they help to restore the skin barrier. Often indifferent semisolid bases themselves or their lipid and lipoid components have an emollient effect. Frequently suitable compounds that increase the general effect of the preparation have been added – natural moisturizing factors (urea, lactic acid, glycerol and others) and compounds increasing skin protection (silicon oil, dimeticone). Epithelizing agents support epithelium formation and healing at local application. **Alpha tocopherol acetate** *(Tocoferoli alfa acetas)* and **dexpanthenol** *(Dexpanthenolum)* are available as epitelization stimulating agents, and **fish oil** *(Jecoris aselli oleum)* as a compound containing A and D vitamins. An example of an indifferent protective ointment intended for e.g. paw pads in dogs is formula No. 6.

Formula No. 6: Protective ointment for paw pads in dogs

Tocoferoli alfa acetas	2.0
Dimeticonum	10.0
Vaselinum album	ad 100.0

Anti-inflammatory drugs

Ichthammol *(Ichthammolum)* has usually been incorporated into liquid, semisolid and solid topical dosage forms. **Beech tar** *(Fagi pix)* and **bismuth tribromophenate** *(Bismuthi tribromphenolas)* are other anti-inflammatory agents that are parts of Višněvski balsam *(Balsamum Višněvski cum pice liquida)*. With its anti-inflammatory and healing effects, **Peru balsam** *(Balsamum peruvianum)*, that can be incorporated into many topical dosage forms, is a component of the other type of Višněvski balsam, in that the Peru balsam substitutes for the beech tar *(Balsamum Višněvski cum balsamo peruviano)*. **Dimethyl sulfoxide** *(Dimethylis sulfoxidum)* has strong anti-inflammatory and analgesic effects and enhances the local penetration of drugs in topical preparations[1, 4, 5].

Local anesthetics

The selection of local anesthetic compounds is quite wide, and a newly available **lidocaine** (base) *(Lidocainum)* has been added to the earlier obtainable compounds **benzocaine** *(Benzocainum)*, **procaine hydrochloride** *(Procaini hydrochloridum)*, **cocaine hydrochloride** *(Cocaini hydrochloridum)*, **trimecaine hydrochloride** *(Trimecaini hydrochloridum)*, **dibucaine hydrochloride** *(Cinchocaini hydrochloridum)*, **tetracaine hydrochloride** *(Tetracaini hydrochloridum)* and **lidocaine hydrochloride** *(Lidocaini hydrochloridum)*. For anesthesia of the skin, benzocaine and lidocaine (base) have been used, for mucosal anesthesia lidocaine, trimecaine, tetracaine, for anesthesia in infiltration and draining procaine, trimecaine, and lidocaine. For the eyes lidocaine and tetracaine can be used, but most frequently oxybuprocaine has been used[6]. However, oxybuprocaine is obtainable just as a mass-produced product. For anesthesia of the skin only anesthetics as bases need to be used, e.g. lidocaine emulgel[7]. For infiltration and draining anesthesia and for the eyes, anesthetics as salts (most frequently hydrochlorides) must be used.

Decongestive drugs

Decongestive drugs have been used as symptomatic medicine (e.g. in vasomotoric rhinitis therapy). The range of registered products in human medicine is wide, but compounded decongestive agents solutions of bigger package size are economically interesting. **Xylometazoline hydrochloride** *(Xylometazolini hydrochloridum)* is a decongestive agent newly available for compounding, and shows just a direct alpha-1--sympathomimetic effect, in contrast to **ephedrine hydrochloride** *(Ephedrini hydrochloridum)*, and in contrast to **adrenaline tartrate** *(Epinephrini tartras)*, xylometazoline is stable in aqueous milieu and shows a longer-term decongestive effect.

Beta blockers and calcium channels blockers

Propranolol hydrochloride *(Propranololi hydrochloridum)* and **sotalol hydrochloride** *(Sotaloli hydrochloridum)* are non-selective beta blockers without intrinsic sympathomimetic activity (ISA) newly available for compounding that can be incorporated into oral (aqueous solutions, hard capsules, oral hydrogels) and topical (skin hydrogels[8]) preparations. **Verapamil hydrochloride** *(Verapamili hydrochloridum)* and **nifedipine** *(Nifedipinum)* are calcium channels blockers newly available as well.

Antiemetics, prokinetics

Domperidone *(Domperidonum)* is a newly available substance that can be incorporated into oral (aqueous suspension, hard capsules) or rectal (suppositories, sticks) dosage forms.

Sedatives and hypnotics

Chloralhydrate *(Chlorali hydras)*, **phenobarbital** *(Phenobarbitalum)*, **phenobarbital sodium** *(Phenobarbi-*

talum natricum) and **diazepam** *(Diazepamum)* are still obtainable for compounding, **promethazine hydrochloride** *(Promethazini hydrochloridum),* a sedative-like antihistamine drug, and **midazolam** *(Midazolamum)* are newly available for extemporaneous preparation. Midazolam can be converted to a water soluble salt that can be incorporated into solutions.

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ZPRÁVY

41. mezinárodní kongres pro dějiny farmacie v Paříži

Tradice největšího nadnárodního odborného setkání farmaceutických historiků pokračovala i v roce 2013. Mezinárodní kongres pro dějiny farmacie, který ve dvouletých intervalech pořádá Mezinárodní společnost pro dějiny farmacie (ISHP) a Mezinárodní akademie pro dějiny farmacie (AIHP), byl v pořadí již 41. a tentokrát se konal v Paříži 10.–14. září 2013.

Lokálním organizátorem byla Francouzská společnost pro dějiny farmacie, která byla založena v roce 1913 jako první vědecká organizace, orientovaná na farmaceutickou historii. Její 100. výročí vzniku zároveň inspirovalo i jedno z ústředních témat kongresu, kterým byl vznik a vývoj historie farmacie jako vědního oboru. Dalšími tematickými okruhy v souvislosti s dvoustým výročím úmrtí významného francouzského lékárníka, vojenského farmaceuta a polyhistora A. A. Parmentiera (1737–1813) byly vojenská farmacie a činnost farmaceutů-lékárníků v různých oblastech mimo farmacie.

Výsledky práce historiků farmacie ze všech koutů světa byly prezentovány v rámci pěti plenárních přednášek a 150 přihlášených příspěvků, jejichž polovinu tvořily přednášky, přednesené postupně ve třech paralelních sekcích. Dalších sedm desítek příspěvků bylo prezentováno formou posterů, které byly ke zhlédnutí po celou dobu kongresu v prostorách konventu Cordeliers (dnes součást Lékařské fakulty Univerzity Paříž V). Program kongresu byl doplněn odbornými exkurzemi, společenským setkáním účastníků a slavnostním shromážděním AIHP.

Na kongresu byli formou aktivní účasti přítomni i členové Sekce dějin farmacie České farmaceutické společnosti ČLS JEP. Prezentovali tři postery: Výuka dějin farmacie v České republice (autoři: J. Babica, L. Valášková a V. Rusek); Česko-francouzské vztahy v minulosti (autoři: P. Drábek a M. Lisá); Vznik českých farmaceutických družstev a jejich hospodářská a společenská činnost v letech 1835–1948 (autoři: V. Vranová, M. Lisá a V. Rusek) a dvě přednášky: Záložní nemocnice Červeného kříže v Kuksu 1914–1919 (autoři: L. Valášková a L. Svatoš); Počátky vysokoškolské výuky dějin farmacie v bývalém Československu (autor: T. Ambrus).

V závěrečný den kongresu byly prezentovány některé aktuální aktivity ISHP a s pozváním na následující kongres do Istanbulu v roce 2015 vystoupili jeho organizátoři, kolegové z Turecka.

T. Ambrus