Veterinary medicine: safe and effective for the animal being treated – safe for people and the environment

Paths of treatment in multiple sclerosis

Increased use of corticosteroids as nasal decongestants
The small market for veterinary medicines in Finland poses challenges for the authorities and the veterinary medicines industry. The industry operates on business economic principles. On the one hand, there is – understandable – reluctance to offer for sale unprofitable products. On the other hand, necessary medicines should be available to veterinarians. Pet owners are prepared to pay more and more for the treatment of their pets, and demand up-to-date methods of treatment. It would benefit everyone to have on the market veterinary medicinal products with marketing authorisations so that their quality, safety and efficacy are appropriately assessed, and they are sold with appropriate instructions for use on the packaging. At present, the problems in availability of veterinary medicines are being patched up with the special license system.

The control of veterinary medicine has many special characteristics: There are many animal species, from dogs and cows to fish and chickens; the medicine may end up in the environment (e.g. medicine for fish) and cause harm to the environment. The consumer may be exposed to residues of medicine which have made their way into food, and the person administering medication may react adversely to the substance. Many veterinary medicines are immunological products, i.e. vaccines. There are safety risks related to vaccines, as well: A live vaccine may contain a virus that does not belong there. Such a virus would not pose a problem, if it were already present in the country, but a virus of foreign origin could cause serious outbreaks of animal diseases in Finland. In these cases, for instance, the National Agency for Medicines utilises a wide external network of experts.

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The human safety is one of the important issues receiving special attention in the control of veterinary medicines. The medication of food-producing animals can result in residues of the medicine present in food-stuffs made of the animal in question, and that could be harmful for the consumer. For this reason, special attention has traditionally been paid to setting the withdrawal periods for veterinary medicines in Finland and the other Nordic countries. In Finland, the withdrawal periods for old medicines were reviewed in 1999, while their marketing authorisations were renewed. It would seem that the EU is gradually adopting the method of assessing the withdrawal periods of new medicines practised by the Nordic countries.

The operator safety is another very important issue when assessing the safety of veterinary medicines. The operator may, for example, be exposed to external parasite medication or preparations applied by nebulization (spraying), containing sensitising agents. Correct instructions for dosage and use protect the operator; it is therefore important to read the instructions in the package insert before administering the medicine.

The third important issue pertaining to the safety of humans is the drug resistance related to antimicrobial drugs, which knows no boundaries between humans and animals. In both the EU and the USA, heated debates are being waged about whether the use of fluoroquinolone antibiotics on food-producing animals imperils the health of humans. In countries where fluoroquinolone have been used in the treatment of poultry, the resistance to salmonella and campylobacter has rapidly become more prevalent. This can exacerbate the treatment of salmonella and campylobacter in humans. In Finland, the situation with regard to resistance is still good. Experts serving the National Agency for Medicines have actively participated in the work of EMEA's (The European Agency for the Evaluation of Medicinal Products) Veterinary Medicine Committee in preparing guidelines for antimicrobial drugs, and have emphasised the importance of maintaining a good resistance status. It seems that this work is slowly bringing results.

Translation Liisa Fellman-Paul
Summary

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Paths of treatment in multiple sclerosis

Until the mid-1990s only symptomatic treatment was available for multiple sclerosis (MS). Relapses associated with MS are significantly reduced (about 30%) by drugs introduced in the 1990s which probably to some degree also prevent the progression of the disease.

At present, various therapies can be chosen from Table 1 below, but there is no obligation to start any medical treatment at all, because the efficacy of all the treatments available is still only partial.

Table 1. Therapy alternatives.
1. Immunomodulatory therapy
2. Cytostatics
3. Intravenous immunoglobulin
4. (Plasmaphaeresis)
5. Cortisone pulse therapy

Immunomodulatory therapies: interferon beta and glatiramer

Interferon beta-1b and -1a, and glatiramer acetate since 2001, are the first drugs capable of influencing the course of MS and not simply alleviating the symptoms.

Interferon beta affects the penetrability of the blood-brain barrier and decreases the number of antigen presenting cells, for example, as well as T lymphocyte production. It is unknown at present which of the several effects of interferon beta is the most essential one in the treatment of MS, but a general anti-inflammatory effect and a gamma-interferon antagonist effect are likely. Drugs with an effect on the development of the disease are presented in Table 2.

Introduction of treatment with interferons for remitting, relapsing MS is recommended as early as possible once the diagnosis is confirmed. It appears that interferon beta therapy should be started as early as following the first demyelinating symptom, especially if changes characteristic of demyelination are detected on MRI examination. This is possibly one way of bringing about a significant delay in the change of a probable to a definite diagnosis of MS. Interferon beta also has some effect on the secondary progressive form of MS, especially if relapses associated with the disease continue.

A European study on interferon beta-1b showed a statistically significant prevention of progression of the disease and a reduction in relapses during the study, which lasted for two and a half years. Subsequently, this preparation has also been officially licensed to be used for the indication of secondary progressive MS within the EU area. As shown in Table 3, other studies have not revealed a significant benefit of the interferon beta therapy measured by the EDSS change, which can be considered a conventional method of measuring the efficacy.

There is nevertheless no effective

Table 2. Drugs affecting the development of MS.

<table>
<thead>
<tr>
<th>Substances</th>
<th>Interferon beta-1b</th>
<th>Interferon beta-1a</th>
<th>Interferon beta-1a</th>
<th>Glatiramer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Betaferon</td>
<td>Avonex</td>
<td>Rebif</td>
<td>Copaxone</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>18,5 kDa</td>
<td>22–24 kDa</td>
<td>22–24 kDa</td>
<td></td>
</tr>
<tr>
<td>Recommended dose</td>
<td>250 µg every second day sc.</td>
<td>30 µg x 1/week im.</td>
<td>22 or 44 µg x 3/week sc.</td>
<td>20 mg x 1/day sc.</td>
</tr>
<tr>
<td>Neutralising antibodies</td>
<td>38 %</td>
<td>5–19 %</td>
<td>22 µg: 23.8 %</td>
<td>44 µg: 12.5 %</td>
</tr>
</tbody>
</table>


**Table 1.** Therapy alternatives.

1. Immunomodulatory therapy
2. Cytostatics
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4. (Plasmaphaeresis)
5. Cortisone pulse therapy

**Table 2.** Drugs affecting the development of MS.
Glatiramer acetate is a polypeptide compound which, similarly to the interferons, has been found to reduce the frequency of exacerbations in remitting, relapsing multiple sclerosis by about 30%. It can be used as primary treatment for multiple sclerosis, especially if elevation of liver enzymes or severe depression occurs during interferon therapy, or if neutralising antibodies develop and the response to interferon is concurrently reduced. Glatiramer has no effect on the progressive form of the disease either. Nor have antibodies which would reduce the effect of treatment with glatiramer been found to develop, and it has the smallest number of adverse reactions in comparison to the immunomodulatory therapies available. Changes in kidney function have been reported in association with the therapy, and it is consequently recommended that creatinine values be monitored at least at the start of treatment.

The most important adverse reaction of interferon beta is a feeling similar to that of a ‘flu attack which will pass within 4–12 hours. At the start of interferon beta therapy, the condition of some patients will temporarily become worse, but it is usually restored to normal within 1–2 months. Liver function tests are monitored during treatment, because elevation of hepatic enzymes and hepatitis occasionally occur. If the hepatic enzymes are elevated, the dose of interferon beta should be reduced or the therapy interrupted until the hepatic enzymes are restored to normal. Increased risk of infections or malignancies has not been found. However, any globally wider experience of interferon beta therapy only dates back 7–8 years. Interferon beta therapy should not be administered during pregnancy, and it is recommended that the treatment be withdrawn a month before unprotected sexual intercourse.

The efficacy of treatment is undergoing evaluation at present to find out whether it is influenced by the administration route (subcutaneous or intramuscular) and frequency of administration chosen (once weekly versus three times a week or more often). The conclusion drawn from studies published during the last year is that increasing the dose will increase the efficacy up to a certain point.

In the first study of interferon beta-1b, the efficacy of 1.8 million IU every second day did not differ from the placebo treatment, but the same study showed that the efficacy of 8 million IU every second day was significantly more effective than 1.8 million IU doses and the placebo treatment. On the other hand, the interferon beta-1a therapy revealed that 44 µg x 3/week during 2 years was not superior in efficacy when compared with a dose of 22 µg x 3/week measured as EDSS changes, but after 3–4 years of the same study the difference was also shown clinically, and the administration of 44 µg x 3/week was slightly more effective in comparison with the lower dose (1). MRI monitoring showed a difference in efficacy between the doses after as few as 2 years of monitoring and the difference was maintained during 3–4 years of monitoring to the advantage of the higher dose.

Fewer neutralising antibodies to interferon are apparently manifested after intramuscular administration than after subcutaneous administration. Preliminary results also suggest a clinical significance for the neutralising antibodies, since the effect of treatment in antibody-positive patients was reduced whereas it remained unchanged in antibody-negative patients. A study of interferon beta-1a also showed that an increase in the dose from 30 µg to 60 µg once a week produces no improvement in efficacy.

Direct comparisons between interferon beta preparations showed Betaferon 250 µg every second day to be more effective than Avonex 30 µg once a week (2). Similarly, preliminary results of Rebif 44 µg x 3/week compared with Avonex 30 µg once a week indicate somewhat superior results with the higher dose (3).

### Cytostatic treatment

The first alternative to interferon beta or glatiramer treatment could be the use of azathioprine (2.5 mg/kg, orally) to prevent relapses and exacerbations of MS. Azathioprine has been shown to prevent relapses, but there are no data concerning the effect on the demyelination complexes in the brain based on the MRI, and there are no data about its efficacy in the prevention of the progression of the disease (4, 5, 6). The dose of azathioprine is 50 mg x 2–3 and the treatment should continue for a minimum period of 6 months until the clinical efficacy can be assessed. The blood count and hepatic enzymes should be monitored during azathioprine therapy. Reported adverse effects include leukopenia, lymphopenia, allergic reactions, pancreatitis, activation of latent infections and possibly a slightly increased risk of lymphoma.

Another alternative is mitoxantrone (12 mg/m², intravenously

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study, N</th>
<th>Primary Endpoint</th>
<th>Subgroup Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>European SPMS study</td>
<td>D-B, pl-contr. multi-c N=718</td>
<td>+ progr. of MS (EDSS) (21.7%)</td>
<td>+ effect shown in all subgroups</td>
</tr>
<tr>
<td>SPECTRIMS study</td>
<td>D-B, pl-contr. multi-c N=618</td>
<td>- progr. of MS (EDSS)</td>
<td>+ relapsing pat. 44 µg x 3</td>
</tr>
<tr>
<td>US SPMS study</td>
<td>D-B, pl-contr. multi-c N=939</td>
<td>- progr. of MS (EDSS)</td>
<td>+ relapsing pat. all IFN doses</td>
</tr>
<tr>
<td>Nordic SPMS study</td>
<td>D-B, pl-contr. multi-c N=300</td>
<td>- progr. of MS (EDSS)</td>
<td></td>
</tr>
<tr>
<td>IMPACT study</td>
<td>D-B, pl-contr. multi-c N=436</td>
<td>+ progression of disab. (MSFC)</td>
<td>+ progression of disab. (EDSS)</td>
</tr>
</tbody>
</table>
and every 3 months) for the prevention of relapses and progression of the disease. In the studies, mitoxantrone was administered either alone or in combination with methylprednisolone. The indications for mitoxantrone can be considered to consist of very active remitting, relapsing MS with no response to interferon beta or glatiramer acetate, and of active relapsing progressive or secondary progressive MS. Treatment with mitoxantrone has shown significantly reduced frequency of relapses and reduced progression of the disease measured by the EDSS scale. These findings are also supported by MRI examinations (7). The use of mitoxantrone is restricted by its cumulative cardiotoxicity (maximum total dose 120–140 mg), which is why its most appropriate use is found in the treatment of severe conditions such as halting a severe progression and alleviating a frequently relapsing disease. Once the situation has calmed down preventive immunomodulatory therapy can be reinstated.

**Intravenous gammaglobulin**

Yet another alternative for use in the treatment of exacerbations of MS is a massive intravenous dose of immunoglobulin. Doses of 0.15–0.2 g/kg once a month, 0.4 g/kg for 5 days followed by 0.4 g/kg every second month, and 2 g/kg once a month, have been used in various studies; all of these regimes have shown an even greater reduction of relapses than was shown with interferons or glatiramer, and a slightly reduced progression. In comparison with the placebo, the frequency of lesions aggravated by gadolinium was found to be significantly reduced (8, 9, 10). Since the treatment is extremely expensive, the use is restricted to special circumstances.

Plasmapheresis therapy has also been studied in the treatment of MS. It may be tried if an acute state of exacerbation is not relieved by other methods of treatment.

**Treatment with steroids**

An acute exacerbation or a relapse of multiple sclerosis is treated with methylprednisolone if the new neurological symptoms caused by the disease, or a sudden significant exacerbation of the old symptoms fulfil the criteria of a relapse. Cortisone pulsing is used for the treatment of those states of exacerbation which significantly reduce the ability to function. Milder symptoms can also be treated if they are not beginning to show spontaneous improvement. The treatment consists of intravenous administration of 1–1.5 g methylprednisolone on 3–5 consecutive mornings. Another method is oral administration of 400 mg on three consecutive mornings as a so-called “home pulsing” to a patient who has previously received several intravenous pulses without complications. It is not medically justified to supplement these steroid pulse treatments by routinely tapering low doses of cortisone. In the treatment of optic neuritis, compared with the placebo or small-dose treatment with tablets, the best improvement of sight was obtained with intravenous methylprednisolone. The treatment with tablets in small doses did not differ from the placebo. There is no proof of the efficacy of steroids in the long-term prognosis of multiple sclerosis (11).

**Literature**


3. Fàrkílá M and the EVIDENCE study group. The Evidence study: Direct comparative study on IFN beta 1 a three times weekly (Rebif) and once weekly (Avonex) in RRMS. 17th Congress of of the European Committee for treatment and Research in Multiple Sclerosis (ECTRIMS), Sept.2001, Dublin, Ireland.


Increased use of corticosteroids as nasal decongestants

Topical decongestants can be divided into sympathomimetics, corticosteroids, antiallergic agents (excluding corticosteroids) and other nasal decongestants.

Sympathomimetics decongest the nasal mucosa and decrease the mucosal secretion. Their continuous use may nevertheless cause rebound mucosal swelling and continuous nasal congestion, and the maximum period of use is 5–10 days. The most effective treatment for allergic nasal congestion consists of corticosteroids which are used for both seasonal and perennial rhinitis. Treatment for seasonal rhinitis is introduced prior to exposure and continued for the entire duration of exposure. Drops of vitamin A, or of sodium chloride in small children, can be used for moisturising the nasal mucosa.

A large proportion of nasal decongestants are over-the-counter preparations. All sympathomimetics are available at the pharmacies without prescription. A nasal spray containing sodium cromoglicate, one of the group of antiallergic agents, has been used in self-care since 1992, and levocabastine, an antihistamine, since 1996. The first OTC nasal corticosteroid spray was introduced on to the market in 1996.

Total consumption

During the last ten years, there has only been a slight increase in the consumption of topical nasal decongestants (ATC Code R01A). In 1990 their consumption was over 14 defined daily doses (DDD), and in 2001 it reached over 19 DDD per 1,000 inhabitants. About a half of these were used in self-treatment. Calculated on the basis of DDD, topical nasal decongestants are used more frequently in self-treatment than are cough or cold preparations. In 2001 they were bought at retail prices to a value of over EUR 5 million.

Among topical nasal decongestants, the consumption of corticosteroids has increased the most (Fig. 1). The growth was slow until the mid-1990s, increasing thereafter. The increased consumption was influenced by beclomethasone becoming an OTC preparation in 1996. The consumption of sympathomimetics had been falling, but it has turned into a slight rise during recent years. A consumption peak was to be seen in 1993, when several sympathomimetics were available on the market. The consumption of antiallergic agents increased slightly after 1992 when the nasal spray of sodium cromoglicate became an OTC preparation. The consumption has remained stable ever since, and the release of levocabastine on to the OTC market in 1996 has had no effect on total consumption of this group of drugs.

Seasonal fluctuation in consumption

The consumption graph of corticosteroids reveals a significant increase in consumption of the more recent introductions on to the market and of other corticosteroids (other corticosteroids = mometasone and triamcinolone) (Fig. 2). The consumption of older drugs, budesonide and beclomethasone, has decreased. The consumption of fluticasone has in recent years amounted to about a third of the total consumption of corticosteroids.

The consumption of corticosteroid preparations is significantly increased during the spring-time allergies (Fig. 3). The sale of both prescription and OTC preparations is increased during March-April and correspondingly decreased during July-August when the exposure to allergens is reduced. The consumption of other antiallergic agents is steady with only a small peak seen in the spring.

The winter-time ‘flu period leads to a peak in the consumption of sympathomimetics in February, and the consumption is reduced in the summer and increased again in the autumn when the new ‘flu period starts. The increase in consumption is brought about especially by the increased sale of xylometazoline preparations.

The monthly consumption graphs also show an increased consumption of nasal moisturising preparations in the autumn and winter.

Based on the monthly consumption graphs in 2001, it can be claimed that the use of topical nasal decongestants appears on the whole to be reasonable. Sympathomimetics are used mostly during ‘flu periods, the use of corticosteroids is concentrated on the periods of allergy, and other preparations – including nasal moisturising preparations – are also used as alternatives.

References


**Figure 1. Consumption of nasal decongestants (ATC Code R01A).**

**Figure 2. Consumption of corticosteroids.**

**Figure 3. The monthly consumption of nasal decongestants in 2001.**