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Special permits to fill the gaps in the availability of medicines

In Finland, the number of medicines with marketing authorisation is constantly growing, and therefore the range of medicines available is greater than ever before. Despite that, situations arise now and then where suitable treatment is not available, and the medicine needed for treating a patient does not have a marketing authorisation. The Medicines Act makes allowance for such exceptional cases. It provides for a special permit being issued to an unauthorised medicine for administration to a specific patient for particular medicinal purposes.

The plethora of individual special permits for compassionate use – 17 000 decisions per annum – raises the question of whether the need for medicines lacking marketing authorisation at such a great rate is genuine and warranted. A closer inspection of the permits reveals that, contrary to assumptions, the underlying cause is not so often the need to resort to an extraordinary, special form of treatment, but rather regular treatment of a small group of patients.

Some of the special-permit medicines have never been granted marketing authorisation in Finland, either due to the medicine being at an early stage of clinical use, or the rarity of the illness. After the marketing authorisation of a medicine has been cancelled on health or safety grounds, its use may well be warranted as the therapy of choice for individual patients under certain

circumstances. Particularly in these cases, the responsibility and expertise of the treating physician is emphasised, when deciding on the course of treatment. The acquisition of correct information on the efficacy and safety of a medicine might in such cases be laborious, because of which the supervision of the treatment requires greater care than usual.

It is worth noting that one third of all special permit decisions concerned medicines whose marketing authorisations had expired as a result of decisions made by pharmaceutical companies. Old, relatively unpopular medicinal preparations, the sales of which are no longer considered competitive, are constantly being removed from the market. Product ranges, their variety of strengths and dosage forms, are now more than ever before under strict critical scrutiny for competitiveness. As a result, some of our long-established drug treatments are finally excluded from the marketing authorisations system. This phenomenon occurs easily in small language and market areas such as Finland. The only means available to the National Agency for Medicines for influencing the retention of a medicine on the market is exempting it from the annual marketing authorisation fee.

Summary

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New approaches in the treatment of Crohn's disease

Even though the aetiology and pathogenesis of Crohn's disease remain unknown, the disease has been the object of intensive medical research. Novel biological response modulators have been introduced in clinical practice and the position of old drugs such as 5-ASA preparations has been reviewed. The new biological drugs are effective albeit costly, and they require well-defined patient treatment plans including, above all, objective indicators of the response and criteria for continuing the treatment. The aims of treatment are also changing: as well as freedom of the patient from symptoms, endoscopic response to treatment is also an objective. Endoscopic remission has been found to improve the patients' quality of life and to decrease hospitalisation as well as, naturally, the need for surgery.

Crohn's disease is a chronic inflammatory bowel disease which may involve the entire gastrointestinal canal, even though the changes are more generally situated at the end of the small intestine and in the caecum and ascending colon. Cases involving the small intestine exclusively total about 30%, and those involving the large intestine exclusively total about 25% of all the cases. According to the clinical picture, the disease is defined as stricturing, fistulous and non-perforating, non-stricturing, or of the colitis type (Vienna classification); the selection of medical treatment also depends on the subtype of the disease. According to present understanding, Crohn's disease is an immunoregulatory bowel control disorder in genetically susceptible individuals, characterised by a triggering factor, usually a bowel infection, and as a result of which the immunological tolerance to the normal intestinal bacterial flora is destroyed. This results in a continuous active inflammatory response, and due to the increased permeability of the intestinal mucosa the intestine "leaks" bacterial antigens, which again in their turn activate the T lymphocytes and macrophages of the lamina

propria. The apoptosis of the activated T lymphocytes is normally an important control mechanism of the inflammatory response, which in Crohn's disease is reduced, thus maintaining and increasing the chronic state of the inflammation. The activating macrophages of the T cells increase the inflammatory reaction even further, producing proinflammatory cytokines, such as interleukin 1, TNF and interleukin 12. A chronic active inflammation results in tissue injuries and abdominal pain, diarrhoea and bleeding. The incidence of Crohn's disease is 14–15 times greater in first degree relatives than in the unrelated, and the concordance of monozygotic twins vis à vis the disease is 67%. The first gene exposing the patient to the disease, CARD 15, has been found on chromosome 16. It explains a relatively small proportion of the origin of Crohn's disease and the specification of the mutation has no clinical significance in the assessment of the prognosis or the treatment of the disease.

Medical treatment

The medical treatment of Crohn's disease remains empirical. Two ap-

proaches can be distinguished: 1) alleviation of the active disease, i.e. induction of remission and 2) maintenance treatment of the remission (Table 1). The planning of the treatment requires a definitive diagnosis of the disease and a review of the extent, activity and potential complications of the disease. In addition to symptoms, the diagnosis is, to a large extent, based on endoscopic examinations. Evaluation of response has for a long time been based on various indices of symptoms, the most commonly used one of which is the CDAI (Crohn's disease activity index). Numerous indirect indicators determined from the serum or the faeces (e.g. calculation of calprotectin, α 1-antitrypsin and lactoferrin levels in the faeces) have been developed which could replace endoscopic examinations.

Induction of remission

Corticosteroids constitute the primary treatment of active Crohn's disease (1, 2). As many as 80% of the patients achieve a clinical remission through oral prednisolone therapy within 4 weeks (3, 4). In the induction of remission, budesonide at 9 mg/day is almost as effective as

Table 1. The treatment of active Crohn's disease. Induction of remission.

<i>Location of disease</i>	<i>Primary therapy</i>	<i>Secondary therapies</i>
<i>Ileocaecal/ileal disease</i>	<i>Prednisone, budesonide</i>	<i>Antibiotics, sulfasalazine glucocorticoids, azathioprine, infliximab</i>
<i>Colon/colorectal disease</i>	<i>1) metronidazole 2) sulfasalazine 3) 5-ASA (postoperatively)</i>	<i>Antibiotics, glucocorticoids azathioprine, mercaptopurine, infliximab</i>
<i>Fistulous disease</i>	<i>metronidazole, azathioprine, infliximab mercaptopurine</i>	

prednisone 40 mg, but it has fewer adverse reactions. Budesonide is nevertheless appropriate only in the treatment of the terminal ileum and/or the ascending colon in Crohn's disease, whereas neither of the corticosteroids is superior to a placebo in the maintenance treatment of the disease. Metronidazole among the antibiotics has been proven effective in colitis or ileo colitis in active Crohn's disease, but apparently not in the form of the disease involving exclusively the small intestine (5, 6). The efficacy of aminosalicyclic acid (5-ASA) preparations in active Crohn's disease is very small. Six randomised placebo-controlled studies (7) have been published on the efficacy of mesalazine in mild and moderate Crohn's disease; a significant difference vis à vis the placebo was only found in two of them, in which a daily dose of ≥ 3.2 g was used. In the studies which compared mesalazine with prednisone the response to the 5-ASA preparations was found to be significantly poorer (7). Consequently, sulfasalazine and mesalazine are rather more appropriate in the maintenance treatment of mild ileocolic Crohn's disease or Crohn's colon. Ciclosporin has been found to be ineffective in active Crohn's disease.

Immunosuppressive treatment with, for instance, azathioprine or methotrexate is of no great importance in the acute state of the disease due to the slow response to them. They are nevertheless excellent in the treatment of the chronically active disease and in maintenance treatment, and the therapy is usually introduced already at the acute stage in combination with

drugs to induce remission (compare: treatment of remission).

The concentrations of tumor necrosis factor alpha (TNF α) are elevated in Crohn's disease. TNF α is a proinflammatory cytokine which partakes in e.g. the activation of macrophages and the cytokine synthesis thereby potentiating the inflammatory response. TNF α antibodies promote the apoptosis of the activated T cells, thereby also interrupting the inflammation cascade. Good results have been obtained with a TNF α antibody, infliximab, in the treatment of active moderate to severe Crohn's disease resistant to treatment. A clinical response (a drop of over 70 points in CDAI) was obtained with a single infusion (5 mg/kg) in 81% of the patients, compared with 17% obtained with a placebo, and remission (CDAI below 150) was achieved in 33% and 4% of the patients, respectively, within four weeks (8). Good results have been obtained in fistulous active Crohn's disease by using intravenous doses of infliximab 5 mg/kg in series of 0, 2 and 6 weeks (9). About 50% of the active fistulas

close up after a series of three infusions administered over a period of six weeks.

Maintenance of remission

The induction of a remission is successful in the majority of acute cases of Crohn's disease, but the maintenance of remission is considerably more difficult.

Drugs used in the maintenance treatment of Crohn's disease are outlined in Table 2, the most commonly used and most effective ones of which are the immunomodulators: azathioprine and mercaptopurine, and also methotrexate.

Thiopurines

A meta-analysis of the efficacy of azathioprine and mercaptopurine in the treatment of Crohn's disease shows the efficacy of thiopurines in the active disease to be 3.09-fold (95% CI 2.35–3.91), and in the maintenance of remission it was shown to be 2.27-fold (95% CI 1.76–2.93) compared with the placebo (10). They have also been found effective in the treatment of fistula and thus constitute the primary treatment in the chronically active fistulous disease (10). When using adequate doses, it is also possible to achieve a complete endoscopic remission with thiopurine therapy (11). The recommended doses are: azathioprine 2.0–2.5 mg/kg/day and mercaptopurine (MP) 1–1.5 mg/kg/day. Azathioprine is a prodrug which is nonenzymatically metabolised to mercaptopurine. Somewhat fewer dyspeptic adverse reactions are associated with mercaptopurine (Table 3). Seri-

Table 2. Maintenance of remission in Crohn's disease

<i>Location of disease</i>	<i>Primary therapy</i>	<i>Secondary therapies</i>
<i>Ileocaecal/ileal disease</i>	<i>azathioprine, mercaptopurine</i>	<i>methotrexate, infliximab</i>
<i>Colon/colorectal disease</i>	<i>metronidazole, sulfasalazine 4–6 g azathioprine</i>	<i>methotrexate, infliximab</i>
<i>Fistulous disease</i>	<i>metronidazole, azathioprine, mercaptopurine, fluoroquinolones</i>	<i>infliximab</i>

Table 3. The main undesirable effects of drugs used in the treatment of Crohn's disease

Drug	The most common adverse reactions
Sulfasalazine	Headache, abdominal pain, nausea, rash, fever, hepatitis, haemolytic anaemia, leucopenia, agranulocytosis, pancreatitis
Mesalazine	Headache, nausea, diarrhoea, pancreatitis, hepatitis, interstitial nephritis
Corticosteroids	Moon face, acne, osteoporosis, weight increase, striae, hypertension, hyperglycaemia, cataract
Thiopurines	Nausea, abdominal pain, rash, leucopenia, pancreatitis, hepatitis
Methotrexate	Nausea, abdominal pain, bone marrow depression, stomatitis, tiredness, fever, hepatitis, pneumonitis, teratogenic
Infliximab	Immediate: infusion reactions, dyspnoea, rashes, urticaria, anaphylaxis, nausea, diarrhoea, abdominal pain Delayed reaction: increased sensitivity to infections, opportunistic infections, changes in hepatic values, autoantibodies, clinical picture of the SLE type

ous adverse reactions associated with thiopurines have resulted in the withdrawal of treatment in about 9% of clinical studies. The most common adverse reactions include allergic reactions, bone marrow depression (2–3%) and pancreatitis (3–7%). In theory, the mercaptopurine metabolite, thioguanine (at 40 mg/day), may have fewer adverse reactions compared with mercaptopurine and azathioprine, but it also causes leukopenia and hepatic enzyme elevation as well as pancreatitis (12), and there is no proof of safety on long-term use. The primary maintenance treatment of extensive, chronic active or fistulous or densely recurring Crohn's disease is azathioprine or mercaptopurine.

Methotrexate

If the patient does not tolerate thiopurines, the alternative is methotrexate. The proof of its efficacy is nevertheless less assured than that of azathioprine or mercaptopurine. In steroid-dependent (dose \leq 12.5 mg/day for over 3 months) chronically active disease, 39.4% of the patients on intramuscular methotrexate (25 mg/week) achieved a remission calculated by the CDA index and were able to abandon steroid therapy altogether, whereas the corresponding figure in the placebo group was 19.1%. However, the study only lasted for

40 weeks and was not endoscopically controlled (13). 65% of the patients who had earlier responded to methotrexate therapy remained in remission when the methotrexate therapy was continued at intramuscular doses of 15 mg/week, compared with 39% of the patients on placebo (14).

Aminosalicylic acid preparations

The efficacy of mesalazine preparations in the maintenance treatment of Crohn's disease is debatable. A total of 9 randomised placebo-controlled studies of the maintenance treatment have been published comprising about 1,500 patients in all (15). The number of relapses in the placebo group in the studies has varied between 32% and 71% (median of 53%), compared with 22%–64% in the treatment groups (median of 45%). In six of the studies, a statistical difference between the control group and the treatment group was not possible to achieve. The daily doses used were 1–4 g/day, a median of 2.4 g. A meta-analysis (16) showed that in studies where its effect was reviewed the efficacy of mesalazine therapy did not differ statistically from the placebo in the maintenance of remission induced by medical treatment; it was only postoperatively that the 5-ASA preparations were more effective than the placebo in sustaining the

remission. In the light of the benefit shown the present role of 5-ASA preparations in the treatment of Crohn's disease should be critically reassessed. What, then, are the therapeutic indications of these preparations in Crohn's disease? In the treatment of active Crohn's disease, very high doses of sulfasalazine (4–6 g/day) may be effective when treating the mild or moderate colonic type of Crohn's disease, and doses of mesalazine in excess of 3 g may be effective in the treatment in Crohn's disease of the ileum (17). In maintenance treatment, the only definite proof for mesalazine is in the prevention of postoperative relapses at daily doses of 3 g, and consequently, the current extensive, aimless use in maintenance therapy in Crohn's disease is unfounded. Results for Crohn's disease are not available on the chemoprevention of dysplasias or colorectal cancer by the use of 5-ASA preparations.

Infliximab

A study comprising 335 patients has been published on the efficacy and safety of use of infliximab in the maintenance treatment of Crohn's disease (18). The Crohn's disease patients selected had a CDAI of 220–400 and they had responded (a drop of over 70 points in the CDAI) to the first infusion of infliximab 5 mg/kg after 2 weeks of its administration. This was 59% of the original selection of patients. The patients were randomised into three categories of treatment, where one group received a placebo, another infliximab in the 2nd and 6th week and twice thereafter at 8-week intervals. The third group received the same induction therapy, but the maintenance treatment consisted of 10 mg/kg at 8-week intervals. The number of patients remaining in remission (CDAI $<$ 150) was analysed at week 30, and at week 54 the number of patients in whom the disease had recurred was established. 21% of the patients on placebo were in remission, 39% of those in group II (maintenance treatment 5 mg/kg) and 45% in group III (maintenance treatment 10 mg/kg). Compared with the placebo, infliximab therapy (groups II and III) was 2.7-fold (95% CI 1.6–4.6) more effective, but the doses of 5 and 10

Table 4. Recommendation on the use of infliximab in Crohn's disease Helsinki University Central Hospital, HYKS

Therapeutic indications

- extensive or fistulous Crohn's disease not responding to other treatment

Dosage

- non-penetrating disease
two infusions 5 mg/kg at 0. and 8. weeks
- penetrating disease (fistulas)
- three infusions 5 mg/kg at 0., 2. and 6. weeks

Response control

- clinical and endoscopic evaluation of the result of treatment: 4 weeks following the end of the course of treatment

Maintenance treatment

- if response to treatment is objective: reinfusions at 2–4 month intervals

mg/kg did not differ from each other statistically. A relatively high number of adverse reactions occurred, and 9% of the patients withdrew themselves from the study. Infections requiring antibiotic therapy were exhibited in an average of 32% and severe infections in 4% of the patients. 17% of the patients experienced infusion reactions. Based on the results of this study, it can be concluded that the likelihood of patients with active Crohn's disease previously not treated with infliximab reaching remission at week 30 is 23% (5 mg/kg). The achieved response to treatment and its duration are, among other things, influenced by the formation of antibodies to infliximab (19). The antibodies also increase the risk of infusion reactions. The formation of antibodies, again, is influenced by the immunomodulatory medication in use: corticosteroids, thiopurines and methotrexate including the number of infusions administered. Patients on immunomodulatory treatment have fewer infusion reactions, a superior primary response to treatment and a longer duration of response. In addition to the formation of antibodies, smoking significantly decreases the treatment response achieved by both azathioprine and infliximab, actually to such an extent that there is reason to question the treatment with these drugs of a smoking patient with Crohn's disease.

In whom is infliximab therapy justified, then? According to a Euro-

pean (20) and an American (21) treatment recommendation, infliximab is primarily indicated for the treatment of patients in whom other treatments (corticosteroids and immunomodulators) have not produced an adequate response, or if, due to serious adverse reactions, immunomodulatory drugs cannot be used and the disease cannot be treated surgically, or for the treatment of patients with a fistulous disease with no response to customary treatment (20). The criteria for maintenance treatment have nevertheless changed in view of the previous European recommendation. If induction therapy produces a definitive response, then maintenance therapy is justified, but the continuation of treatment in patients who have not responded to treatment is unfounded. A recommendation for a criterion in infliximab therapy to be followed within the Helsinki-Uusimaa Hospital District is outlined in Table 4 (20-22). In the absence of antibodies, adequate immunomodulatory treatment is a prerequisite for the introduction of infliximab therapy. A shift to maintenance treatment requires a definitive response to treatment. It is recommended that response to the maintenance treatment be checked at the latest a year after the start of the therapy series, and a decision be made about any continuation of treatment.

Other TNF α antagonists and inhibitors. CDP571 is a humanised monoclonal antibody of the IgG4

class. Nevertheless, in clinical studies its efficacy has been found to be significantly poorer than that of infliximab. Etanercept is a soluble fusion peptide of the TNF receptor and found to be ineffective in the treatment of Crohn's disease.

Thalidomide inhibits TNF biosynthesis by increasing the TNF mRNA breakdown in the macrophages. The primary treatment responses have been relatively modest, but in maintenance treatment, after the induction of infliximab and when thalidomide was used at 100 mg/day, over 80% of the patients remained in remission for 12 months following the last infusion of infliximab (23).

Further medical treatment in Crohn's disease

The underlying causes of symptoms exhibited by a patient with Crohn's disease may be other than those of disease activation. Diarrhoea after terminal ileum resection may originally be due to malabsorption of the bile salts, and it is effectively treated with cholestyramine or cholestipole. In extensive small intestine resection, fibre products and loperamide may be used to slow down the small intestine transit time and to reduce diarrhoea and increase the absorption of fluids. Replacement of fat-soluble vitamins is justified on the basis of proven deficiencies. Furthermore, patients with inflammatory bowel diseases experience functional abdominal discomfort at least as often as healthy volunteers.

Novel drugs in the treatment of Crohn's disease

Several new biological response modulators influencing the various stages of the inflammatory process are being studied in the treatment of Crohn's disease: antibodies affecting the differentiation of CD 4T helper lymphocytes and lymphocyte mobility, such as natalizumab and new TNF mediated cytokinin antibodies. In future, the treatment of Crohn's disease will be more by individual combination treatment than it has hitherto been. Even though Crohn's disease is not curable at present, the

majority of patients can be made symptom-free and given long-term remission. Endoscopic remission reduces the patient's symptoms, improves the quality of life, and decreases the need for hospitalisation and surgical treatment. Neither will the disease shorten the patient's lifespan.

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Summary

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ADR News

Renal and urinary tract ADRs reported to the National Agency for Medicines during 1973–2003

In view of the total blood circulation in the body, the kidneys are among the most important organs, since adverse drug reactions (ADRs) in them may have serious consequences renal circulation is approximately 25% of the body's total blood circulation, and the kidneys, for their part, are responsible for the elimination from the body of various substances, foreign to the body, and of waste substances introduced via the nutrition. It is estimated that 2–3% of adverse drug effects would be targeted at the kidneys and the urinary tract. The estimate is supported by the reports on adverse drug reactions received by NAM during 1973 – September 2003 (17,608 reports), 2.1% of which were on reactions in the kidneys or the urinary tract.

As with other organ groups, renal toxicity can be distinguished as non-dose-dependent and unpredictable reactions (idiosyncratic renal toxicity), and as predictable dose-dependent adverse reactions (toxicity associated with the size of dose). Direct toxicity is mostly associated either with the direct renal tissue damage caused by the drug, or with changes in the renal blood flow. Medicinal substances known to have dose-dependent adverse effects on the kidneys include e.g. antibiotics of the aminoglycoside group, drugs intended for the treatment of infections or for immunosuppression (amphotericin, ciclosporin and vancomycin), non-steroidal anti-inflammatory anal-

gesics, paracetamol and lithium. In practice, the same drug groups may also cause idiosyncratic reactions. If the patient's renal function is impaired as part of a primary disease, then the groups of exacerbating drugs include e.g. ACE inhibitors, aminoglycosides, anti-inflammatory analgesics, contrast media and angiotensin receptor blockers.

The most commonly reported symptoms and diagnoses associated with renal and urinary tract ADRs included (reported terms in parentheses) symptoms indicative of renal impairment (increased serum creatinine, albuminuria and abnormal renal function), 69 reports; micturition pain, 66 reports; symptoms or diagnoses indicative of direct renal damage (acute or chronic renal failure, anuria, uremia, nephrotic syndrome), 63 reports; histological renal damage (interstitial nephritis, nephritis, renal tubular necrosis and "minimal change" glomerulonephritis), 29 reports; urinary retention, 29 reports; haematuria, 27 reports; and urinary incontinence, 16 reports. Among the reported symptoms, haematuria, for example, can be considered a rather non-specific symptom because, in addition to the administered medicinal substance, it can also be associated with acute urinary tract infection and renal or urinary tract neoplasms.

The reports were fairly evenly distributed among the individual medicinal substances and their respective groups. There were distinctive trends among the ADRs: in-

creased creatinine values associated with the use of ACE inhibitors (14 reports), renal damage associated with anti-cancer drugs and especially ciclosporin, or their symptoms (14 reports), micturition pain or stinging sensation during micturition associated with the use of tolfenamic acid (31 reports), increased serum creatinine or albuminuria associated with the use of aurothiomalate for the treatment of rheumatic diseases (10 reports). Adverse reactions caused by antibiotics were mostly associated with interstitial nephritis, elevated serum creatinine, renal damage or symptoms of the onset of renal damage reported with the use of broad-spectrum penicillin derivatives, cephalosporins and aminoglycosides (20 reports).

On the basis of these ADR reports it is fair to say that renal damage associated especially with drugs that have been in use for a long time is well known in clinical practice, and any new drug safety signals causing alarm cannot be detected among the reported renal or urinary tract ADRs. The evaluation of renal adverse drug reactions or indications of them should therefore in the future focus on the recent medicinal substances, especially those with a tendency to renal accumulation and elimination. In general, dose-dependent toxicity should be monitored especially carefully and each suspected renal reaction reported to the National Agency for Medicines.

Summary

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ADR News

A case of adverse drug reaction

Drug fever caused by hydroxycarbamide

Drug fever is a rare adverse reaction despite its being thought to occur in as many as 10% of hospital patients (1). The connection between fever and an individual drug may be difficult to detect because fever as a symptom is very common; the patient is perhaps being treated with several different drugs at the same time, and a drug used for a long period of time may also suddenly trigger fever. Many unnecessary and costly examinations can be avoided by early diagnosis of drug fever. Our case is a patient who was found to have drug fever which had been triggered by hydroxyurea, i.e. hydroxycarbamide.

Our own case

Our patient is a 55-year-old male who had about seven years previously been diagnosed with a hyper-eosinophilic syndrome associated with skin manifestations. At the time of diagnosis, the blood eosinophil leukocyte count was at the level of $1500 \times 10^6/l$. The patient had no other underlying diseases, nor did his history reveal any allergic tendencies. The hyper-eosinophilic syndrome had been treated with oral prednisolone. It had not been possible, however, to decrease the dose below the daily dose of 15 mg, and since the patient also developed osteoporosis, a decision was made to supplement the treatment with hydroxycarbamide. The dose of prednisolone remained at 15 mg/day up until the 31st of July, and the dose was thereafter reduced by 5 mg. A concomitant dose of 500 mg hydroxycarbamide twice a day was initiated at the same time. The dose was designed to be halved after 10 days.

On the 18th of August, i.e. less

than three weeks after commencement of the treatment, the patient developed a high fever (39°C), headache and myalgia. No nausea, vomiting, skin changes or joint trouble occurred. On arrival at the hospital the following day the patient was feverish (39.3°C), but his general condition was nevertheless fairly good. The conjunctivae were bloodshot. There was no stiffness of the neck, and no other neurological findings were made. The patient was hospitalised in a ward for infectious diseases.

On admission, the laboratory results were fairly normal. The erythrocyte sedimentation rate (ESR) was within normal limits (7 mm/h) and the C reactive protein (CRP) slightly elevated (33 mg/l). The blood count was normal, the total leukocyte count was $6.9 \times 10^9/l$, and an analysis revealed the following: neutrophilic granulocytes 81%, lymphocytes 9%, monocytes 8%, eosinophiles 1% and basophiles 1%. The serum hepatic values were within normal limits, but the lactate dehydrogenase concentration was slightly elevated (508 U/L). Primary examinations on the spinal cord fluid did not reveal abnormalities, and bacterial staining and culture gave negative results, as also did herpes simplex and enterovirus investigation. Epidemic nephropathy or tularaemia antibodies were not detected in the serum, and no significant findings were made on serum virus antibody screening. No abnormalities were revealed in X-rays of the lungs and paranasal sinuses.

The CRP was at its highest on the 20th of August (45 mg/l), when ESR was elevated to 31. Hydroxycarbamide therapy was discontinued on admission to hospital, and treatment with prednisolone was continued.

Fever abated within a couple of days, having been 39.7°C on the 20th, 37.2°C on the 21st and 36.8°C on the 22nd of August, the day of discharge.

The patient took one tablet of 500 mg hydroxycarbamide on the 26th of August. Soon afterwards he developed a fever with shivering and a severe headache, i.e. the symptoms overall bore a close resemblance to the previous condition.

Conclusion

The patient obviously developed a drug fever caused by hydroxycarbamide. A similar reaction caused by re-exposure gives support to the role of hydroxycarbamide. No other cause for the fever could be found. In particular, viral meningitis – with which the symptoms were perfectly concordant – could not be diagnosed.

Hydroxycarbamide is an oral cytostatic which has been in use since the 1960's. Its effect is based on the DNA polymerase inhibition. Hydroxycarbamide is used in haematology, primarily in chronic myeloproliferative diseases, but also in the alleviation of acute myeloblastic leukaemia, and, in very large doses, in association with autologous stem cell transplantation in haematological and non-haematological malignancies (2). It is used for the treatment of sickle cell anaemia (3) and also as an adjunct to other treatment, e.g. in psoriasis and HIV infection. The drug is well absorbed, reaches its peak blood concentration within about two hours and is eliminated from the body within 24 hours. The drug is eliminated via the kidneys. The usual daily dose is between 0.5 and 3 g depending on the patient and indica-

tion, but the very large doses required to achieve aplasia may be as high as 100 mg per kg of body-weight daily (4). The drug is mostly well tolerated and due to its short half-life the dose is generally easy to titrate. The general adverse reactions include bone marrow depression and consequent cytopaenias, gastrointestinal symptoms, impaired renal function and skin reactions.

Rare adverse reactions caused by hydroxycarbamide include febrile reactions (5, 6, 7, 8 and 9). However, in only a proportion of the reported cases has this effect been confirmed by re-exposure. Some of the cases have been associated with influenza-like symptoms and, as in our case, myalgia and shivering. The condition in two patients with psoriasis was complicated by palpable purpura which corresponded histologically to small-vein necrotising vasculitis (5). The time between the start of the medication and the onset of the fever has varied greatly in the reported cases. Lossos and Matzner describe a patient with essential thrombocytosis who developed a fever as quickly as 12 hours after the start of the medical therapy. Moschella and Greenwald (5) describe 60 psoriasis patients on hydroxycarbamide therapy with a follow-up period of 18 months. Six of the patients developed a drug fever (two of whom also developed dermal vasculitis) which in all cases started within six weeks of the start of the medication. The fever typically subsided within a couple of days after discontinuation of the drug therapy.

A drug fever can be triggered by almost any medicine. Numerically, most of the cases have been associated with antibiotic treatment. Johnson and Cunha (1) give a list in their survey of the medicinal substances generally causing drug fever, and these include e.g. amphotericin B, phenytoin, interferon, cephalosporins, quinidine, penicillins, salicylates and sulphonamides. Mackowiak and LeMaistre (10) report on 148 drug fever episodes during 1959–1986. Of these, 51 were compiled from the records of two hospitals in Dallas and the rest from the literature. The article mentions nearly 60 diverse medicines as fever-triggering drugs; one of them is hydrox-

ycarbamide. The list also contains old substances such as alpha-methyl-dopa, procainamide and cimetidine. The time between the start of the medication and the onset of fever varied greatly; on average it was 21 days (median of 8 days). This time was considerably shorter with regard to fever associated with cytostatic agents (mean of 6 days) compared with the other drug groups. The mean onset of fever associated with antibiotic treatment was about 8 days. The drug fever nearly always ceased within 2–3 days of discontinuation of the drug therapy. Only rather rarely was the fever associated with eosinophilia in the blood (22% of the cases) or rash (18%), and every fourth patient exhibited myalgia, 16% exhibited headache. If eosinophilia occurred, it was generally mild. Tendency to atopy, female sex or advanced age did not predispose the patient to drug fever. The researchers did not find any fever type especially typical of drug fever.

There is no definite information on how general fever as the adverse reaction to a drug actually is. It is estimated that fever as the sole adverse reaction would make up 3–5% of all adverse drug reactions (11). Drug fever is probably much more frequent, at least with beta-lactams, compared with other drugs. It is worth suspecting fever associated with antibiotic treatment if, during a long antibiotic therapy lasting for several weeks, the fever attacks continue, or the fever starts again, and if there is no natural explanation for its cause such as antibiotic diarrhoea, abscess or endocarditis. Should rash or eosinophilia occur in the patient at the same time, the diagnosis is usually easy. During drug fever, the patient's general condition typically remains good in comparison with the level of the fever, while shivering and other general symptoms do not exclude the possibility of drug fever (1). Circulating leukocytosis, elevation, significant elevation even, of ESR and CRP, and mild elevation of hepatic values can occur during drug fever.

The drug-fever-inducing mechanism of drugs is unclear. Despite the variety of mechanisms, supported by the significant variation in the required period of exposure and the

fact that the fever can be caused by very varying medicines, the most common mechanism is considered to lie among the various immunological or hypersensitivity reactions caused by the drug (1). It is suggested that the medicinal substance or its metabolite can act as a hapten and, together with the body's own proteins, form antigenic structures. Antigen-antibody complexes can subsequently release endogenous pyrogens and cause fever. A medicinal substance or its metabolite can also react directly with tissue proteins and cause the release of pyrogens. A third possibility is a delayed cell-mediated immune response. Antibodies to the medicinal substance detected in the blood may support the possibility of drug fever, but their absence does not exclude it.

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Summary

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A drug or a foodstuff?

Products with seemingly medical constituents, but for sale not only at the pharmacy but also elsewhere, have recently been confusing consumers. What products are these? Where does the line lie between a foodstuff and a drug, and who supervises what is being sold? This article aims at explaining the legislation and the authorities' supervision associated with the sale and marketing of foodstuffs and drugs.

What is a drug?

A drug is a product or a substance which, when used either internally or externally, has as its purpose to cure, alleviate or prevent a disease or symptoms of a disease in man or animal. It is a product or substance used either internally or externally to reverse, improve or change the vital functions of human beings or animals, or to unravel the reasons for their state of health or disease.

Herbal medicinal products are also considered to be drugs.

... and what is a foodstuff?

In addition to the conventional foodstuffs, these also include the food supplements, i.e. the products that have been supplemented with nutrients, e.g. vitamins, for nutritional purposes. Food supplements covered by the supervision of the authorities of the National Food Agency in Finland form a product group closely related to that of drugs. A food supplement refers to a

ready packed product which is for sale in the form of a compact, capsule, pastille, tablet, pill, powder, concentrate, extract, liquid or other similar type of dose, which is offered for sale as a foodstuff designed to be taken in measured small quantities whose amount of energy is of no significance to the diet.

The package, leaflet, advertising or any other form of presentation of a food substance or foodstuff should not detail any properties associated with the prophylaxis, treatment or cure of human diseases; and no reference should be made to similar information.

The consumer viewpoint

Products containing substance included in the List of medicines issued by National Agency for Medicines can sometimes be sold as foodstuffs. Consequently, on the market there may be different products containing the same substances, the manufacture and sales of which, however, are governed by different requirements depending on whether the products are introduced on to the market in accordance with the drug legislation or the foodstuffs legislation.

Does it matter for the consumer whether he or she buys the product as a drug or as a foodstuff? A valid marketing authorisation is required for all drugs being sold. In order to obtain a marketing authorisation for a drug, there are required reviews of quality, safety and efficacy, which

are evaluated by the authorities. After the approval of the marketing authorisation, the safety of use of the medicinal product is still regularly evaluated. When the consumer buys a drug, he or she is buying a product which has undergone prior evaluation of safety of use, efficacy and quality, and the safety of use of which is being constantly monitored.

Products are classified by NAM upon request

The Agency decides whether a substance or a product should be considered a drug. A classification can be applied for by submitting a classification request, the contents of which are discussed on the website of the National Agency for Medicines. The classification decision is made individually for each product and the product is classified either as a drug, non-drug or a medical device. The decision is influenced by both the constituents of the product and its indication for use. If the product is used according to a drug specification, its indication for use is medical. Further information on the classification procedure and decisions of classification made by the National Agency for Medicines can be found on the Agency's website <http://www.nam.fi/english/laws/classification/application.html>

Once the classification decision is made

Once a product has been classified as a drug, it may not be sold as a foodstuff. A marketing authorisation application must be submitted for a product classified as a drug before it can be introduced on to the market. The entrepreneur is responsible for the sale of his or her product, for the correct choice of a sales channel and for ensuring that the product classified as a drug is removed from the shelves of shops selling foodstuffs. The supervisory authorities may interfere if the product is sold illegally.

Supervision of marketing of medicinal products

Only drugs referred to in the Medicines Act may be advertised or marketed as drugs. Marketing to the public and marketing to health care personnel are distinguished from each other. If the drug marketing involves any illegal procedures, the National Agency for Medicines may impose a ban on any further marketing. The Agency may also stipulate that the party banned from marketing submits a correction of marketing to the Agency if considered necessary in view of drug safety risks. The demand for a correction may be reinforced by a default fine.

In addition to the supervision carried out by the authorities, drug marketing is also governed by independent supervision by the pharma-

ceutical industry itself. Pharma Industry Finland (PIF) is an association promoting issues associated with the industrial policy of the medical research industry. It also publishes drug marketing guidelines in the form of a compilation of advice intended for the use of the pharmaceutical industry itself and based on both national and international legislation governing drug marketing. The member companies of Pharma Industry Finland (PIF) are bound by common consent to follow the guidelines. Within the association, the adherence to the drug marketing guidelines is supervised by the Supervisory Commission for the Marketing of Medicinal Products and, subject to it, two inspection committees. Not all pharmaceutical companies are members of Pharma Industry Finland (PIF).

Important legislation

The Act on Foods (361/1995 including amendments)

Ministry of Trade and Industry Decree on Food Supplements (571/2003)

Decree on the Labelling of Foodstuffs (794/1991 including amendments)

Medicines Act (395/1987 including amendments)

National Agency for Medicines Decision concerning the list of medicinal substances and herbal remedies

Summary

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Medical devices

New coding system for models of endoprosthesis

The aim of the endoprosthesis register by the National Agency for Medicines is to ensure the quality of endoprostheses and the safety of patients in Finland. The purpose of the new registration system for implant data is to improve the contents of information in the register as to serve the development of endoprosthetics.

The results of endoprosthetic surgery have improved considerably during recent years. New implant materials and new resurfacing hip systems have been introduced. A review of the present registration system of endoprosthesis data is necessary in order to reach the aim in the best possible way. Several publications and indisputable proof are available of the benefits of analysis of registered endoprosthetic data. In the 1990s, following the results of Norwegian and Finnish analyses, a few cementless prostheses were removed from use owing to poor stability.

Up until now the registration of implant data has been based on short codes used for inserting the implant data into the endoprosthesis register. The codes have not always indicated the manufacturer, the importer or the material of the implant. The additional information associated with the code has often consisted only of the name of the model. In the original coding system, all implants by one and the same manufacturer were coded with the same initial number, but this coding system was subsequently abandoned owing to the large number of implant models.

Common codes were initially designed for the various parts of hip and knee prostheses, but the system was changed in 1996 to separate storage of the various parts. Information on the internal parts of the acetabular liners of hip prostheses or femurs heads have nevertheless not been registered separately. This has

created a problem as different parts can be combined fairly freely.

For the design of the system and outlining of the various needs, consultation was sought, for example, with representatives of arthroplasty surgery, implant importers and bar code companies. There are in total 13 implants import companies in Finland.

Implant model register and other improvements

More detailed information on implants will in the future be extensively collected in the model register, the information collection system will be improved and the data contained in the register will be expanded.

The data on implant models fitted after 1996 have been inserted in the model register with their old codes. The new coding system will be based on the use of product numbers (reference numbers) for each implant. The model register will contain information on all parts of the endoprostheses, details of manufacturers and importers and also details on the material, design and fixing properties of the implants. The model register will in future allow for the analysis of durability curves in accordance with each individual property of the endoprosthesis. Data on different fixing cements, commercial bone transplant preparations and core plugs will also be available from the register. It is important to focus attention on the monitoring of bone transplant products, because associated legislation is under preparation.

Information on implants in the endoprosthesis register will be in the form of product numbers, on which the model register is based. The use of product numbers will ensure the correctness of implant product information.

The report forms will be reviewed

and a separate form will be designed for each prosthesis. Electronic versions of the report forms will be prepared.

In future, each implant will also have a lot number stored, by which each item inserted during an operation can be identified and traced down to the manufacturing date and lot. Packaging bar codes (product and lot numbers) can also be used for storing, which reduces defects. All different parts of the prostheses will be stored with their own specific product and lot numbers, which will also improve the quality of the information. New report sheets will also be introduced for improved accuracy in the storing of information regarding bone transplants and fixing materials.

The planning of the reformed register has been focussed especially on the question of which issues would be most appropriately stored nationally and which ones should be associated with the data collected at the actual operation unit. In the work of reform, particular attention has been directed at the correctness of data in the model register. It is important that in future the details of each new model be obtained from the importer and made available in the model register even before the endoprosthesis is introduced on to the market and its sale begins in Finland.

Consequently, collection of data for the model register has already begun. It is intended for introduction by the summer of 2004. A review of the report sheets will begin thereafter. The new forms will in future also be used for the registering of data on new implants (hip fracture prostheses, vascular prostheses, spinal prostheses and cochlear implants).

Translation Mervi Moisander