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Summary

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Editorial

From words to deeds to get the message across – more reliable drug information is needed

In a report submitted to the Ministry of Social Affairs and Health, The National Agency for Medicines (NAM) suggested that a new, national drug information centre, based at NAM, should established in Finland. The centre would function independently and apart from NAM, but making use of its services. As a separate centre, it would be under the economic control of the Ministry of Social Affairs and Health. The centre is envisaged to be initially manned by eight experts, and to have an annual budget of about 8 million Finnish marks (1,3 M EUR) in 2002. It would be fully financed by appropriations from the national state budget.

In the background to the above-mentioned report was the often in the 1990s felt need for qualitative improvements of drug therapy in accordance with knowledge derived from research. This plan was recently been developed further under the project known as ROHTO. The objective is to collect, summarise and disseminate to health care professionals – especially physicians – any information promoting rational and cost-efficient drug therapy. The purpose would be to modify prescribing practices along the lines of the knowledge made available to the profession.

The primary function of the planned centre would be to evaluate new medicines on the market, with the emphasis on their therapeutic status and significance for the economy as a whole. The information disseminated by the centre should help the physician to decide where to fit in the new medicines in his "arsenal" of useful and preferable medicines, thus balancing the effect of commercially available information. This activity is intended to exert influence and to modify physicians' prescribing practices.

Making use of broad networks of experts, and collaborating with research institutes and scientists would be the main types of activity of the national drug information centre. In addition to using traditional media, electronic publishing methods could be made use of in disseminating information. Regional co-operation networks should also be established, and existing contacts could, naturally, be used.

Practical evidence both in Finland and abroad suggests that the information on research findings disseminated by the pharmaceutical industry itself can be selective, failing to give a full picture of the benefits and disadvantages of a medicine. It is essential for the functioning of the planned centre that it should be able to use and publish the data on clinical studies and other information submitted to NAM by the pharmaceutical industry in the course of the marketing authorisation procedure. Information on pharmacovigilance databases and drug reimbursement statistics, as maintained by the competent authorities, would be additional sources of relevant background information for the centre. Gaining access to the above-mentioned "tools" calls, of course, for political goodwill in the form of legislative reforms. Denmark, for instance, is an encouraging example of such a development, as a similar centre is already functioning there.

The question which will now be asked is, could NAM's function as a collector and provider information on medicines simply be extended, and could it be financed with the revenue of fees from industry or from the national state budget? The credibility and the transparency of the use of fees from the industry are mainly at issue here. It would be difficult to authorise a pharmaceutical product and consequently adopt a very critical attitude vis-à-vis the said medicine. In addition, it should be born in mind that the fees payable to NAM by the pharmaceutical industry are intended to cover only the costs arising from the processing of specific marketing authorisations.

If there were genuine interest in establishing a national drug information centre independent of commercial interests, now would be a good time to take action. The will to do that, which seemed to have a broad base while the proposal was drawn up, is now needed. Funds are also needed, but the necessary sum would fall below 2 per mill of the sum total paid annually in drug reimbursements.

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Summary

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Interactions of tramadol with antidepressants

Two thirds of patients suffering from chronic pain exhibit symptoms of depression. A quarter of them will also fulfil the diagnostic criteria for it. Combination treatment with tramadol and an antidepressant is common in these patients.

Tramadol

The analgesic efficacy of tramadol in chronic pain is based on a weak opioid effect and mechanisms that increase the availability of serotonin (5-HT) and noradrenaline (NA) in the synapse. Tramadol inhibits serotonin and noradrenaline re-uptake at the presynaptic nerve endings, and stimulates the release of 5-HT from them. General adverse effects caused by tramadol include nausea, vertigo, tiredness and headache. Adverse effects can prevent effective long-term treatment, especially in elderly patients.

Antidepressants

All antidepressants on the market affect the re-uptake or metabolism of serotonin or noradrenaline, or of both. Furthermore, the older tricyclic antidepressants also have several receptor effects (muscarinic and histaminic) which may decrease patient compliance because of adverse effects. In the treatment of chronic pain such systems may also have analgesic effects.

Selective serotonin re-uptake inhibitors (SSRI) act by inhibiting the serotonin transporter which transfers serotonin back to the cell at the presynaptic nerve ending. SSRI-type drugs on the market include fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram. In small doses (≤ 75 mg/day), venlafaxine is mainly a serotonin re-uptake inhibitor, but in larger doses it also inhibits the re-uptake of noradrenaline. Nefazodone is both a 5-HT re-uptake inhibitor and a 5-HT2 receptor antagonist. Reboxetine is a selective noradrenaline re-uptake inhibitor but its direct effects on the 5-HT system are very minor. Mianserin and mirtazapine also increase 5-HT and NA transmission.

Pharmacodynamic interactions

In theory, it is possible that the effects of both serotonin and noradrenaline increase and reach a harmful level when tramadol and antidepressants are used concurrently. Adverse effects of serotonin have been described when tramadol has been used together with fluoxetine, paroxetine or sertraline (Table 1). In these cases the prevention of the CYP2D6-mediated metabolism of tramadol partly explains the possible interaction (see Pharmacokinetic interactions).

Even though case reports on the co-administration of moclobemide and tramadol have not been published, with the exception of one where a patient died due to a serotonin syndrome after an overdose of moclobemide, clomipramine and tramadol, this combination should be regarded with extreme caution. It certainly causes increased serotonin release, and the cell uptake and metabolism are inhibited. Serotonin may be responsible for severe adverse effects in some patients even at normal dose levels.

The combination of amitriptyline and other tricyclic antidepressants with tramadol may potentiate each other's serotonergic and noradrenergic effects. The doses of amitriptyline used for treating pain are very small (10–50 mg/day), and problems of interaction with tramadol are probably rather rare.

As with SSRI drugs, tramadol can also lower the seizure threshold, and this may be accentuated when they are administered together. A recent case report refers to a patient who was treated at hospital with tramadol, venlafaxin, prometazin and paracetamol; the morning after discharge from hospital the patient started having seizures as a result of which patient died. All tricyclic antidepressants including mianserin and maprotiline lower the seizure threshold.

Lithium, which is specifically used for a bipolar affective disorder, also has serotonergic effects, and consequently may also increase the adverse effects of serotonin when used concurrently with tramadol.

The effect of polymorphism of CYP2D6

Tramadol is metabolised via CYP2D6 to the M1 metabolite. 5–10% of the population are slow metabolisers due to polymorphism of this enzyme, 1–10% are ultra rapid, and the rest are rapid metabolisers. The concentrations of the substrate are on average higher in slow metabolisers than in the so-called rapid metabolisers. The difference is not, however, very significant, and this is evidently due to alternative metabolic pathways. But the concentrations of (+)-M1 metabolite, which has an opioid effect

Table 1. Summary of case reports from the literature of the patients with suspected serotonin syndrome

Report/patient	Other drugs	Dose & duration of SSRI	Dose & duration of tramadol	Symptoms/ duration	Therapy & result
Mason & Blackburn, *1997, female 42 yrs asthma, backache severe depression*	*metaproterenol 10mg x4 po., pravastatin 20mg, triamcinolone inh. x 4 chloroxazone 250mg x 4 omeprazole 20mg, paracetamol 325mg 1–2 x 4-6, terfenadine 60mg x 2*	*sertralin, dose? > one year*	*300mg/day 3 weeks*	*Atypical chest-pain, sinustachycardia 140/min, confusion, psychos, agitation, sweating, tremor, duration: 3 weeks, fluctuating*	*Situation was dissolved in 24–36 h, when tramadol was withdrawn and sertralin dose halved to 50 mg/day*
Kesavan & Sobaia *1999, female 31 yrs fibromyalgia, endometriosis*	*?*	*fluoxetin 40mg/day 3 yrs*	*400mg/day ca 2 weeks*	*tremor, headache, agitation, anxiety, blefarospasm, fever, sweating, speech problems, high S-prolactin, duration: 10 days, fluctuating*	*procyclidin, clonazepam and diazepam started, fluoxetin and tramadol were withdrawn symptoms relieved in 7 days, total recovery in 2 months*
Lantz & al., *1998, female 78 yrs, severe depression, osteoporosis, fractures of dorsal vertebrae, macular degeneration*	*multivitamins*	*paroxetine 20 mg/day, duration?*	*150 mg/day, 3 days*	*nausea, sweating, irritability, myasthenia, confusion, fever, tachycardia duration: 3 days*	*paroxetine and tramadol were withdrawn, recovery in 4-5 days*
Lantz & al., *1998 female 88 yrs, bipolar affective syndrome, hypertension, coronary artery disease, glaucoma*	*valproate 250mgx2, quinapril 5mg x1, timolol eye drops, ASA 50mg x4*	*paroxetine 10 mg/day, 2 years*	*200 mg/day, 2 days*	*nausea, sweating, vomiting, sleeplessness, vertigo duration: 2 days*	*cyproheptadine 2 mgx3, paroxetine and tramadol were withdrawn, recovery in 4-5 days*
Egberts & al., 1997 *male 47 yrs, depression, arthralgia*	*no other drugs*	*paroxetine 20 mg/day, 4 months*	*100 mg/day (one tablet)*	*shaking, sweating, muscular tics, loss of consciousness duration: 12 hours*	*tramadol was withdrawn, paroxetine dose halved, patient regained consciousness in 12 hours, recovery in 1 week*

200 times higher than that of the substrate, can vary by a factor of ten between slow and fast metabolisers. The analgesic effect of tramadol in opioid responsive pain may be low in slow metabolisers.

Pharmacokinetic interactions

Many antidepressants such as fluoxetine, paroxetine and venlafaxine are substrates for CYP2D6. Concentrations of these drugs may be considerably higher in slow metabolisers compared with fast metabolisers, which will increase the serotonergic effects, and as regards venlafaxine and tricyclic antidepressants also the noradrenergic effects. The elimination of fluvoxamine may also be significantly reduced in slow CYP2D6 metabolisers. Even though, unlike in fast metabolisers, the CYP2D6 inhibitor does not increase the tramadol concentrations in slow metabolisers, the monoamine effects of both tramadol and the above-mentioned antidepressants are potentiated owing to higher concentrations of both drugs.

In the case reports outlined in Table 1, the interaction of tramadol especially with paroxetine and fluoxetine may relate to the pharmacokinetic interactions. Fluoxetine and especially paroxetine inhibit the tramadol-metabolising CYP2D6 enzyme and, consequently, the concentration and serotonergic effects of tramadol are increased.

Small doses of tricyclic antidepressants, particularly amitriptyline, are widely used in patients with neuropathic pain. A depressed patient with pain can be prescribed a small dose of amitriptyline for pains and an SSRI drug for depression concurrently, especially if he/she suffers

Table 2. Cases of death reported to NAM where the patients have used tramadol concurrently with antidepressants.

Patient	*Medication*	*Symptoms*	*Concentration of tramadol. Therapeutic level 0.1–0.3 mg/l*	*Other drug concentrations*
Female 83 yrs, fell, surgery due to hip fracture, was recovering from surgery	*tramadol 200mg/day, doxepine 100mg/day enalapril, furosemid, amoxicillin, doxicillin, methotrexate 5mg/day, ketoprofen, insulin*	*found dead, cause of death: tramadol intoxication*	*4.4 mg/l*	*doxepin: 0.7 mg/l (therapeutic level 0.03–0.15 mg/l)*
Male 79 yrs	*tramadol, perphenazine, levomepromazine, paracetamol+codeine, amitriptyline (dosage?)*	*found dead at home*	*1.4 mg/l*	*amitriptyline 0.1 mg/l (therapeutic level < 0.2 mg/l*
Male 72 yrs	*tramadol, moclobemide, dextropropoxyphene (dosage?)*	*died during hip operation, cause of death: fat embolism*	*0.8 mg/l*	*dextropropoxyphene 0.4 mg/l, moclobemide 2 mg/l*
Male 22 yrs	*tramadol (dosage?), sertraline 50 mg/day*	*after one week of use, loss of consciousness and convulsions of 1 min duration*		

from adverse effects with the larger doses of amitriptyline which are required for the treatment of depression. Tricyclic antidepressants are prone to CYP2D6-mediated interactions, and the concentrations may increase significantly when administered together with a CYP2D6 inhibitor (e.g. paroxetine). Consequently, their serotonergic and noradrenergic effects will also be potentiated. From the pharmacokinetic point of view, sertraline and citalopram are probably the safest antidepressants among the SSRI drugs for use with tricyclic agents.

Patients also often have other diseases and drugs which may increase the adverse effects of tramadol and antidepressants (Table 2).

Adverse effects of serotonin

In the majority of patients who experience adverse effects at the start of treatment the effects will, when the treatment is continued, cease or decrease significantly within 1–2 weeks. Nevertheless, some patients will have significant adverse effects already at small doses. Common adverse effects of serotonin-selective drugs include nausea, loss of appetite, muscular tics, sleep disturbances, anxiety and problems of sexual performance. When the adverse effects are severe the condition is, with certain reservations, called serotonin syndrome. Sternbach requires that at least three of the following symptoms should be present at the same time: change in the state of psyche/consciousness, agitation, myoclonus, hyperreflexia, sweating, tremor, diarrhoea, coordination disturbance and fever. The clinical picture can have a close resemblance to malignant neuroleptic syndrome, and it can be fatal. In practice, the risk of serotonin syndrome is almost non-existent if SSRI drugs are used in therapeutic doses. The condition may develop as a result of a significant overdose, or if another agent with a serotonergic effect is used at the same time.

The symptoms of serotonin syndrome may disappear quickly without any actual treatment on withdrawal of the serotonergic drug. Severe cases may even require intensive care treatment.

Conclusion

When tramadol and antidepressants are prescribed for the same patient, the possibility of their interaction should be considered. Relatively few reports have been published on severe interactions in combined treatment with antidepressants and tramadol. They should nevertheless be taken seriously since they are conceivable on the basis of the pharmacokinetic properties and pharmacodynamic effects of these therapeutic substances. When we take into consideration the possible problems caused by interactions of tramadol and antidepressants, patients will no longer be exposed to unnecessary adverse effects. It is recommended that the prescription of tramadol be avoided in patients on moclobemide therapy. Sertraline and citalopram of the SSRI group of drugs are probably the safest to use concurrently with tramadol, due to the significantly lower CYP2D6 enzyme inihition they show compared with other drugs. The pharmacodynamic potential of an interaction is nevertheless the same with all SSRI preparations, and therefore, none of them can be considered risk-free.

Summary

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Register of adverse drug reactions in 2000

The National Agency for Medicines received 713 reports of suspected adverse drug reactions (ADR) during the year 2000. A total of 377 (53%) of them were serious. The total number of reports was slightly smaller than the year before but the proportion of serious reactions has increased somewhat. The reports are distributed fairly evenly among various drugs; 10 or more reports were received for only 12 substances. The table is not a list of the most harmful drugs and it cannot be used for a comparison of safety between the various substances. Reports on all ADRs are invited especially on new drugs, and this results in a greater number of reports on those than on many old familiar drugs. The list also contains such old drugs which often cause serious ADRs, or the associated safety aspects of which have often been discussed.

The list is headed by a second generation antipsychotic, clozapine, of which the majority of reports (65%) concern granulocytopenia or agranulocytosis. This reaction is well-known; changes in white blood cell count occur in about 1% of patients on clozapine therapy. Due to the frequency and severity of these adverse effects, a white blood cell count and differential count must be done before clozapine therapy is started. Leukocyte counts should be monitored weekly for the first 18 weeks of the therapy, and at least once a month thereafter. The amount of clozapine prescribed should not exceed the amount required between two leukocyte counts. The patient should be reminded to contact a physician immediately if any symptoms of infection appear, such as fever or sore throat.

The majority of ADR reports received among antibacterials concerned levofloxacin, which is a fluoroquinolone antibiotic. Fourteen of the reports were on tendinitis or rupture of the Achilles tendon. Tendinitis caused by fluoroquinolones was discussed in TABU for the first time in 1996. Since then the ADR register has received a total of 42 reports on tendinopathies caused by fluoroquinolones, over a third of which were ruptures of the tendon. The use of fluoroquinolones has increased by about 75% since 1996. Levofloxacin is responsible for the major part of this increase. It has been marketed in Finland since mid 1998.

From year to year quite a large number of ADR reports have been received on nitrofurantoin, which is used in urinary tract infections. During 2000 a total of 21 reports were submitted concerning this drug, two thirds of them associated with lung reactions, most commonly pulmonary infiltrates or pulmonary fibrosis. Three of the cases were fatal. These patients were 71–92 years of age and they had used nitrofurantoin as prophylaxis against chronic urinary tract infections. Due to the possibility of severe pulmonary reactions, patients on nitrofurantoin therapy should be under special monitoring with respect to any pulmonary symptoms such as cough and/or dyspnoea.

The most frequently reported substances in the register of adverse reactions 2000 received by the NAM

Drugs	*Number of reports*
clozapine	*31*
levofloxacin	*25*
nimesulide	*25*
nitrofurantoin	*21*
terbinafine	*15*
iopromide	*15*
valproate	*14*
atorvastatin	*13*
sulfasalazine	*10*
fluvastatin	*10*
rofecoxib	*10*
vigabatrin	*10*

Among antifungal agents, the majority of ADR reports were associated with the use of oral terbinafine. Most of them were reports of various itching skin reactions. Taste disturbances associated with terbinafine therapy have also been reported.

The majority of ADRs among nonsteroidal anti-inflammatory drugs were associated with nimesulide. Over half of the reports were associated with liver reactions, either elevation of liver enzymes (5 cases) or hepatitis (8 cases). There has been a big increase in the use of nimesulide because it is claimed to be a rather selective COX-2-inhibitor and to cause fewer gastrointestinal ulcers than older anti-inflammatory drugs. Owing to its liver

reactions, the product information on nimesulide was updated last year. The SPC (summary of product characteristics) contains a warning, for instance, that patients with abnormal liver function test values and/or symptoms indicating liver damage, should be carefully monitored and the medication should be withdrawn. These patients should not be re-exposed to nimesulide. A short review on liver reactions associated with nonsteroidal anti-inflammatory drugs was recently published in TABU.

In 2000, a total of 16 suspected ADRs were reported to have been associated with the new COX-2 selective anti-inflammatory drugs, coxibs, 10 of which were associated with the use of rofecoxib and 6 with celecoxib. Reports associated with celecoxib therapy were most commonly of various allergic reactions and skin rashes. The use of rofecoxib was associated with isolated reports of oedema, haematuria, pruritus, nausea and vomiting. Treatment with rofecoxib was associated with gastric ulcer in one patient; the patient was on concurrent low-dose ASA therapy. Two cases of suspected interaction were reported for rofecoxib administered concurrently with warfarin: the anticoagulation effect of warfarin had been potentiated in one, and reduced in the other. It is known from previous experience that rofecoxib may prolong the thromboplastin time (INR) in patients on warfarin. The response to oral anticoagulants should therefore be carefully monitored, especially at the start of rofecoxib therapy or when the dose is changed. Due to possible interactions, the blood coagulation activity should also be monitored carefully in patients receiving concurrent treatment with celecoxib and warfarin. Rofecoxib was introduced onto the Finnish market at the end of 1999 and celecoxib half a year later.

Among cholesterol synthesis preventing statins, the majority of ADR reports received were associated with the use of atorvastatin and fluvastatin. Typically reported ADRs of both drugs included muscle pains, elevated creatinine phosphokinase and liver enzyme values. There has been a big increase in the consumption of statins in Finland since the mid 1990's. Both atorvastatin and fluvastatin are among the three most frequently used statins at present.

Iopromide is an iodine-containing contrast medium with low osmolality which is used for angiography, urography and computer tomography. A total of 15 ADR reports were received in 2000 by NAM. The majority of them involved allergic reactions (urticaria, anaphylaxis). The SPC recommends that special care should be exercised in patients with hypersensitivity to iodine containing contrast media. Patients with a history of allergy are also inclined to suffer hypersensitivity reactions more readily than others. Efforts to prevent these reactions can be made by administering e.g. antihistamines and/or corticosteroids to the patients before examination.

The majority of reports received among antiepileptic agents concerned valproate. In two cases the number of epileptic seizures was reported to have increased when valproate was administered concurrently with meropenem. Meropenem is an antibiotic used for the treatment of severe infections and it may decrease the serum concentration of free valproate. Four ADR reports involved fetal valproate syndrome in a child where the mother had used valproate during pregnancy. Valproate is considered somewhat to increase the risk of foetal abnormalities and cause neural tube defects. Epilepsy as such will also increase the frequency of abnormalities, and untreated epilepsy may be associated with seizures which present a risk for both the mother and the foetus. Since some antiepileptic drugs can decrease the serum folic acid concentration or expose to neural tube defects, attempts can be made to reduce the risk of these defects by administering folic acid tablet during the planning of a pregnancy and the first trimester.

Ten ADR reports were submitted last year about vigabatrin, all of them dealing with visual disturbances. Vigabatrin is known to cause permanent narrowing of the visual field in at least a third of patients. Due to the defects in the visual field use of the drug has been restricted, and vigabatrin can nowadays be used in combination treatment for epilepsy only in cases where all alternative appropriate drug combinations have proven insufficient in efficacy or are poorly tolerated. Vigabatrin is also used in children as monotherapy for infantile spasms. The visual field should be mapped out before treatment, and monitoring of the visual field should be repeated at six-monthly intervals during treatment. It is only rarely possible to perform visual field examinations on children under the age of 9. The visual capacity of all children should nevertheless be assessed and children should be sent for examination by an opthalmologist as necessary.

Ten ADRs were reported for sulfasalazine. The adverse effects were typical for sulfasalazine: six cases of hematological disorders, three cases of liver reactions and one case of skin rash.

Translation Mervi Moisander