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The manufacture of medicines is subject to licence. To ensure that the manufacture of the medicinal products is appropriate is one part of the evaluation of marketing authorisation applications. It is the responsibility of the competent authorities in EU member states to ensure that the pharmaceutical industry complies with the mutually agreed Good Manufacturing Practices (GMP), and that the medicinal products on the market are also in practice manufactured in accordance with the marketing authorisation. Implementation of GMP-requirements is an integral part of safety of medicinal products, which is supervised by regular inspections of pharmaceutical manufacturing plants.

Even outside the EU, the manufacturers of medicinal products intended for the EU market are required to comply with the EU GMP-requirements. The inspecting of these pharmaceutical plants relies on co-operation between member states.

The structural changes in the pharmaceutical industry during recent years pose new challenges to the supervisory authorities. These days, the manufacturing processes of medicines have been divided into part processes, many of which are delegated to subcontractors. It is now increasingly common that several manufacturers are jointly responsible for the various processes in the production of medicines; one plant is responsible for the production of the active pharmaceutical ingredient, another one processes e.g. the tablets, a third one packs the medicine, a fourth one performs the quality control testing, while the fifth one releases the medicine on the market. Furthermore, the production of medicines is increasingly being transferred to countries with cheap labour. Although the holder of the marketing authorisation is situated in the EU, the medicine may actually be produced outside the EU. Authorities need to be aware of the problems arising from the above mentioned practices.

Professionals of marketing authorisation documentation and filing within the EU are capable to fulfill authorities’ formal requirements concerning the content of documents and files. Responsible persons participating in the production of medicines in pharmaceutical plants on the other side of the world do not necessarily know how the manufacturing process has been described in the marketing authorisation, or what are the GMP-requirements in the EU for the manufacture of the medicine in question. It has actually happened that an inspector has been taken to a totally different plant than to the one stated in the marketing authorisation. A further cause for concern are cases, where the applicant for marketing authorisation after announcement of coming inspection immediately reports to transfer the production to another plant. To ensure the safety of pharmaceuticals is, with reason, more than just an assessment of the written documentation.

As part of the inspection team of the EU supervisory authorities, the inspectors of the Finnish National Agency for Medicines (NAM) perform inspections on behalf of the whole EU. Once a foreign pharmaceutical plant is included in NAM’s inspection program, the NAM remains in charge of the evaluation of the manufacturer’s GMP-compliance for as long as the relevant marketing authorisation is in force. NAM’s inspection program covers, in addition to domestic ones, pharmaceutical plants around the world, for instance in the USA, India and Japan.

In future the inspection activities are expanding even more. In addition to the regulations concerning authorised medicinal products, there are already statutory GMP requirements applicable at Community level for investigational medicinal products used in clinical trials. In connection with the review of Community legislation, similar requirements will also be applicable to the manufacturer of active pharmaceutical ingredients. Once the new legislation comes into force, NAM’s inspectors will inspect, in addition to the domestic active pharmaceutical ingredients manufacturers, also pharmaceutical plants situated outside the EU, in accordance with the EU’s standards. The increasing and active co-operation of inspectors in EU will, with the harmonisation of GMP requirements and interpretations, also cover these sub-sectors of pharmaceutical industry.

Translation Sari Jay
With drug consumption rising in all age groups the proportion of the elderly population in the consumption-related figures is rapidly growing (1). As the consumption mounts the concomitant use of several drugs is becoming more common all the time, and as high a proportion as 15% of the elderly on multi-drug therapy suffer from undesirable drug interactions (2).

The most important risk of and condition for developing interactions is the concomitant use of two or more drugs. In addition to drugs, patients (and healthy individuals) also use various herbal medicinal products, alternative ‘natural products’, functional food, and other products containing pharmaco-logically active ingredients. It is recommended that the physician asks his/her patient about the use of all the above-mentioned products. The attending clinician should be informed about any special diet the patient may be on.

Considering the extensive use of multi-drug therapies, the number of serious drug interactions is relatively low (3). By identifying the risk factors leading to interactions, the situation may be brought under control. The risks of interactions between medicinal substances can be divided into two groups: factors induced by drugs and factors induced by the patient. Drug interactions appear mostly when two or more risk-carrying drugs are administered to the patient at risk.

What is a risk-carrying drug?
Interactions are classified as pharmacokinetic and pharmacodynamic interactions according to the mechanisms by which they are generated.

A pharmacokinetic adverse reaction develops because the plasma drug concentrations are changed. A pharmacodynamic interaction develops in the target structure (receptor) of the drug without changes in the plasma drug concentrations. For the understanding of interactions it is important to distinguish the drug either as “an inducer drug” or “a target drug”. A target drug is a drug which causes an undesirable effect following a change in its concentration in the plasma (in the body). The inducer drug is, as its name suggests, the element which changes the kinetics or dynamics of the target drug in such a way that an undesirable effect is produced (3).

Since the target drug is the inducer of the final undesirable effect, its characteristics are the crucial indicators of the seriousness of the adverse reaction (4). There are large variations between different drugs in this respect. Even a small change in a plasma warfarin concentration may cause haemorrhages (increased concentration) or prevent a response to treatment (decreased concentration). However, drugs with a wide therapeutic spectrum, e.g. antimicrobials of the penicillin group, do not produce undesirable effects despite even large changes in their concentrations in plasma.

It should be borne in mind that the inducer drugs can be found in any therapeutic group with greatly varying characteristics. Well tolerated drugs such as itraconazole and erythromycin may be important inducers of interactions. The key risk-inducing characteristics of a target drug are presented in Table 1.

The first three characteristics mentioned are those most important in practice because the dangerous effect, steep dose response and dose dependent toxicity can cause an adverse reaction in the patient leading at the worst to death. On the other hand, prevention of response, e.g. reduced analgetic effect of codeine as a result of prevention of the CYP2D6 enzyme, seldom poses a danger to the patient in practice. Drugs which increase the medicinal substance metabolism inhibit in particular the effect of oral contraceptives, the possible result being pregnancy despite regular use of the contraceptive pill (5). Phenytoin is an example of a medicinal substance, the metabolism of which, and consequently the elimination of which from the body, become saturated even at therapeutic doses. Fortunately, this happens with only a few medicinal substances.

### Table 1. Risk-inducing characteristics of medicinal substances

<table>
<thead>
<tr>
<th>Risk-inducing characteristic</th>
<th>Example of a drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dangerous effect</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Steep dose response</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Dose dependent toxicity</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Prevention of response</td>
<td>Codeine</td>
</tr>
<tr>
<td>Prevention of prophylaxis</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Metabolism which becomes saturated</td>
<td>Phenytoin</td>
</tr>
</tbody>
</table>
What puts a patient at risk?

Several factors, dependent on the patient, influence the risk of occurrence of drug interactions. The most important factors include the patient’s age, diseases and the structure of the genes affecting the drug response (Table 2). Several different clinicians attending to the patient at the same time is also a risk factor.

### Table 2. Risk-inducing characteristics of patients

<table>
<thead>
<tr>
<th>Risk-inducing characteristic</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Newborn, an elderly patient</td>
</tr>
<tr>
<td>Organ function impairment</td>
<td>Impaired hepatic and renal function</td>
</tr>
<tr>
<td>Additional diseases</td>
<td>Gastric ulcer, asthma, dementia</td>
</tr>
<tr>
<td>Abnormal gene structure</td>
<td>Non-functioning CYP2D6 enzyme</td>
</tr>
</tbody>
</table>

#### Organ insufficiency and additional diseases

Many diseases, in particular those which result in hepatic and renal impairment, change the kinetics and dynamics of medicinal substances. Acute and chronic liver diseases may affect the plasma binding of drugs, hepatic blood circulation, drug metabolism, distribution in the body and also the body’s sensitivity to drug effects (9). In renal failure, the renal impairment is, however, a physiological phenomenon; the hepatic function of an 80-year-old is only about a half that of a 30-year-old. Many drugs, the anti-inflammatory analgesics in particular, often impair the renal function even further in the elderly. A distinct difference in practice between hepatic and renal impairment is also the fact that the renal function is easy to measure whereas the hepatic function may be impaired in various ways by several different diseases and the function is difficult to assess (9, 10).

The liver’s capacity for the metabolism of foreign substances is very high, and consequently in practice only very advanced liver disease will significantly change the effects of drugs on the body. Renal impairment is, however, a physiological phenomenon; the hepatic function of an 80-year-old is only about a half that of a 30-year-old. Many drugs, the anti-inflammatory analgesics in particular, often impair the renal function even further in the elderly. A distinct difference in practice between hepatic and renal impairment is also the fact that the renal function is easy to measure whereas the hepatic function may be impaired in various ways by several different diseases and the function is difficult to assess (9, 10).

In addition to the disease being treated, drug therapy should also cover other diseases and conditions which may greatly influence the practicalities of the therapy (11).

### Abnormal gene structure

The final drug response is influenced by several proteins (enzymes, transport proteins, receptors); where there is great variation in the genes which code for them in the population (genetic polymorphism). Several deviant forms (alleles) of these genes which may result in unexpected responses to drugs are, of course, known at present (12). One of the best known examples is probably the liver enzyme CYP2D6, of which an inactive variant occurs in about 7% of the Finnish population. In these individuals, drugs metabolised mainly via the CYP2D6 enzyme are eliminated at a slower rate than normal, which may even result in serious adverse reactions.

It is clearly evident that abnormal gene structures may even cause very serious adverse reactions during drug therapy. The following chain of events is suspected of having caused fatal interactions. The patient is using drug X, which prolongs the QT interval. The elimination of this drug is dependent on the activity of the CYP2D6 and CYP3A4 enzymes. The patient has a genetic deficiency of the CYP2D6 enzyme, and this route of metabolism is not functioning. Up till now all is well, however, as CYP3A4 takes care of the drug metabolism and therefore also the elimination. The patient is then giv-

#### Table 3. The effect of additional disease on the drug therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug which exacerbates the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive tract</td>
<td>Anti-inflammatory analgesics, glucocorticoids</td>
</tr>
<tr>
<td>· mucosal damage</td>
<td>Opioids, anticholinergics</td>
</tr>
<tr>
<td>· constipation</td>
<td></td>
</tr>
<tr>
<td>Neurological and mental diseases</td>
<td></td>
</tr>
<tr>
<td>· epilepsy (convulsions)</td>
<td>Antipsychotics, tricyclic antidepressants, amantadine, caffeine, fluoroquinolones</td>
</tr>
<tr>
<td>· dementia</td>
<td>Anticholinergics (tricyclic antidepressants, several neuroleptics)</td>
</tr>
<tr>
<td>Other diseases</td>
<td></td>
</tr>
<tr>
<td>· asthma</td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>· diabetes</td>
<td>Diuretics, beta-blockers, glucocorticoids</td>
</tr>
</tbody>
</table>
en additional medication, itraconazole, for example, which blocks the CYP3A4-mediated metabolism. This causes the drug X concentration in plasma to rise dangerously high and the patient suffers torsades de pointes. If the same patient also happens to have a genetic mutation affecting the cardiac potassium channel causing liability to prolongation of the QT interval, the conditions are in place for a lethal adverse reaction. This is suspected to have been the case with the use of terfenadine, even though complete certainty cannot be reached with any medicinal substance.

Which drugs should be monitored?

Numerous sources of information on drug interactions are available including fairly complete lists of interacting medicinal substances. Table 4 is a short list of some of the substances which in recent years have been in the forefront as targets and inducers of pharmacokinetic interactions. The table lists some of the most important examples.

Several important interactions which develop on the basis of pharmacodynamics are known in addition to those listed above. Drug combinations with mechanisms to increase the amount of serotonin at the nerve ends have been in the forefront recently. A popular analgesic, tramadol, increases the amount of serotonin and when used concomitantly with antidepressants it may cause an excessive serotonin effect (13).

Conclusion

It is possible to reduce the risks of drug interactions by understanding the risk factors associated with the drug and the patient. The role of genetic factors in the drug adverse reactions and interactions is rapidly becoming clear, and in the future, with the help of genetic tests, we may possibly be able to avoid the use of dangerous drug combinations in sensitive patient groups. The general rule of drug therapy is: avoid using two or more risk-inducing drugs concomitantly in a patient at risk!

Literature


Reports received by the adverse drug reaction register in 2003

Last year, the ADR register of the National Agency for Medicines received a total of 936 reports of suspected adverse drug reactions, almost half of which were serious. At least ten reports were received on twenty-one drugs.

Several of the medicinal substances at the top of the list have been recently introduced on to the market and are therefore usually more frequently the subject of reports than old well-known drugs. The list cannot be used for comparison of safety between the medicinal substances as such because of the great variation in the exposure: more reports may be received on a drug which is frequently used than on a drug which is used more infrequently despite the possibility of equal incidence of adverse reactions.

### Antimicrobials

The largest number of ADR reports concerned an antibacterial agent of the fluoroquinolone group, levofloxacin (30 reports). The majority of them (23) were of adverse reaction in the Achilles tendon (tenonitis or tendon rupture). By the end of 2003, altogether 97 cases of adverse reactions in the tendon were reported, 66 of which had occurred in association with levofloxacin therapy. The majority of the cases involved elderly patients (67±13 years), and 76% were male. Concomitant medication with corticosteroids increases the risk of tendon rupture. If the patient is suspected of having tendonitis, the use of fluoroquinolones should be stopped immediately.

Telithromycin is a new antibiotic of the ketolide group and structurally closely related to the macrolide antibiotics. The drug was introduced on to the Finnish market in mid-2002. Last year a total of 20 ADR reports were made on it, six of which involved a skin reaction; five involved nausea and five visual disturbances. Nausea is listed as a common undesirable effect in the SPC (1–10% of the patients), whereas adverse effects on the skin and visual disturbances are uncommon (0.1–1%). The SPC of telithromycin was updated in 2003 and physicians were warned about the use of the drug in myasthenia gravis patients, because telithromycin may exacerbate the symptoms of the disease.

Nitrofurantoin, used for urinary tract infections, was the subject of a report on 13 occasions. On ten of the occasions the cause of the ADR report was a pulmonary reaction (alveolitis, pulmonary infiltrate or pulmonary fibrosis); one patient was also reported as having dyspnoea. Due to the risk of serious pulmonary reactions, all respiratory symptoms such as cough or dyspnea should be reported to the ADR register.

### The medicinal substances most frequently reported to the ADR register of the National Agency for Medicines during 2003

<table>
<thead>
<tr>
<th>Medicinal substance</th>
<th>Number of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>levofloxacin (Tavanic)</td>
<td>30</td>
</tr>
<tr>
<td>ropromide (Ultravist)</td>
<td>27</td>
</tr>
<tr>
<td>celecoxib (Celebra)</td>
<td>26</td>
</tr>
<tr>
<td>clozapine (several products, e.g. Leponex, Froidir)</td>
<td>26</td>
</tr>
<tr>
<td>rofecoxib (Vioxx, Vioxxakut)</td>
<td>25</td>
</tr>
<tr>
<td>simvastatin (several products, e.g. Corolin, Lipcut, Zocor)</td>
<td>21</td>
</tr>
<tr>
<td>telithromycin (Ketek)</td>
<td>20</td>
</tr>
<tr>
<td>ethoricoxib (Arcxia)</td>
<td>20</td>
</tr>
<tr>
<td>infliximab (Remicade)</td>
<td>19</td>
</tr>
<tr>
<td>terbinafine (Lamisil)</td>
<td>17</td>
</tr>
<tr>
<td>atorvastatin (Lipitor)</td>
<td>15</td>
</tr>
<tr>
<td>quelapine (Seroquel)</td>
<td>14</td>
</tr>
<tr>
<td>risperidone (Risperdal)</td>
<td>14</td>
</tr>
<tr>
<td>ethinylestradiol + ethonogestrel (Nuvaring vaginal ring)</td>
<td>14</td>
</tr>
<tr>
<td>ethinylestradiol + drosiprenone (Yasmin)</td>
<td>13</td>
</tr>
<tr>
<td>fluvastatin (Cane, Lescol)</td>
<td>13</td>
</tr>
<tr>
<td>nitrofurantoin (Nitrofur-C)</td>
<td>13</td>
</tr>
<tr>
<td>venlafaxine (Efexor)</td>
<td>12</td>
</tr>
<tr>
<td>carbamazepine (several products, e.g. Tegretol, Neurotol)</td>
<td>11</td>
</tr>
<tr>
<td>bupropion (Zyban)</td>
<td>11</td>
</tr>
<tr>
<td>mirtazapine (Remeron)</td>
<td>10</td>
</tr>
</tbody>
</table>
noea, occurring in patients on nitrofurantoin therapy, should receive special attention.

As in previous years, the majority of adverse reactions reported concerning antimycotics involved terbinafine tablets (17 reports). The most common reactions included taste disturbances (9) and various skin reactions (5).

**Antinflammatory and antirheumatic agents**

Last year, altogether 78 adverse reactions were reported as having been associated with the use of the COX-2-selective anti-inflammatory analgesics, etoricoxib, rofecoxib, celecoxib and valdecoxib, six of which involved serious haemorrhage or ulcer in the gastrointestinal tract (celecoxib 3, etoricoxib 2, rofecoxib 1). Nearly all the patients involved were elderly, over 70 years of age.

The majority of the adverse reactions associated with celecoxib were various allergic reactions and rashes (11). Symptoms indicative of allergic reactions were also reported during the use of etoricoxib (7). The use of rofecoxib was associated with e.g. oedema, weight increase and/or serum creatinine elevation (7). Two patients on rofecoxib therapy were reported as having suffered from lithium intoxication with the concomitant use of rofecoxib and lithium. The SPC includes a warning about increased plasma lithium concentrations due to non-steroidal anti-inflammatory analgesics, and also about the increased plasma lithium levels reported in the use of rofecoxib.

As in previous years, the most frequently reported antirheumatic drug was infliximab (19 reports), which is used in severe, active rheumatoid arthritis and in Crohn’s disease when, for example, an adequate response has not been achieved with other drugs. The drug was granted marketing authorisation through the centralised procedure of the EU at the end of 1999. The most common reactions included taste disturbances (9) and various skin reactions (5).

**Antipsychotics and antidepressants**

The majority of reports on antipsychotics concerned the so-called second-generation antipsychotics, clozapine (26), risperidone (14) and quetiapine (14). The majority of the reports on clozapine concerned granulocytopenia or agranulocytosis (14). Due to haematological changes, the leucocyte count should be checked before the start of the treatment and regularly during the medication. Hyperglycaemia was reported in two patients who had been on clozapine therapy, and diabetes mellitus in one patient. All the cases were serious and resulted in hospitalisation. Medical associations in the USA have recently reported on the risk of weight increase and diabetes associated with the use of atypical neuroleptics (Diabetes Care 27: 596-601, 2004), which appears to be connected in particular with clozapine and olanzapine therapy. The use of risperidone and quetiapine is also associated with weight increase, but there are discrepant research results regarding the risk of diabetes.

Two patients who had received clozapine were reported as having had a serious cerebrovascular accident.

Adverse reactions reported concerning the use of quetiapine last year included cases of hyperprolactinaemia (2), malignant neuroleptic syndrome (1), orthostatic hypotension (1) and extrapyramidal symptoms (1), which are all typical undesirable effects associated with neuroleptic therapy. One patient on quetiapine therapy was reported as having prolongation of the QT interval associated with life threatening torsades de pointes tachycardia. Prolongation of the QT interval is a potent adverse effect with all neuroleptics, but the most evidence of this effect exists onserpine, thioridazine, pimozide and haloperidol. Pimozide is no longer available on the Finnish market.

Serious neurological adverse reactions caused by risperidone (dystonia, extrapyramidal disorder, tardive dyskinesia) were reported in three patients and malignant neuroleptic syndrome in one patient. The report on two patients was made on account of a liver reaction and on one patient because of a prolongation of the QT interval.

The majority of reports received on antidepressants concerned venlafaxin (12 reports) and mirtazapine (10 reports). Two patients on venlafaxin therapy were reported as having prolongation of the QT interval, and one of them was also found to have torsades de pointes. In addition, the reason for reporting the incident in one patient was unconsciousness, but the report did not reveal further information on any arrhythmia. Two patients on venlafaxin therapy, one of whom was also receiving mirtazapine, were reported as having a serotonin syndrome.

Bupropion, also belonging to the group of antidepressants, was the object of an ADR report on 11 occasions. However, bupropion is not used for the treatment of depression in Finland, but is indicated for patients trying to quit smoking, together with other motivating support measures. Nine of the reports referred to an allergic reaction or a skin reaction.

**Hormones**

The use of one of the new contraceptive products, NuvaRing, which contains etonogestrel and ethinyl estradiol, was reported as having been associated with 13 unintended pregnancies and one pulmonary embolism. There were 13 ADR
New antipsychotics, old adverse reactions

The level of consumption of antipsychotics appears to have remained more or less unchanged for the past 20 years in Finland (Fig.). Since the beginning of the 1990's the increased and stabilised use of clozapine has been reflected in the sales statistics, and, during the last five years, other 'atypical', i.e. second generation, antipsychotics have increased their proportion to over a third of all those used. This is also manifested in the adverse drug reactions register, where there are plenty of reports on older drugs dating back to the first years of the register, but where the new drugs start to appear in recent years. This article aims to review the most common adverse reactions caused by antipsychotics and reported in the ADR (adverse drug reactions) register of the NAM, both during the entire period of 30 years and the past 10 years, i.e. since 1994.

A total of 974 reports have been received by the ADR register on adverse reactions caused by antipsychotics, more than half of which were received during the past 10 years. The number of reports sent in nowadays is consequently higher than before. This probably reflects the increase in the general reporting activity, on the one hand, and, on the other hand, the fact that new drugs are reported on more often than old ones, and, in this instance, that the use of clozapine has increased and, as a result, so have also the adverse reactions caused by it. The figures presented overlap, i.e. several drugs may be under suspicion, and several different harmful effects be mentioned, in one and the same report.

The complete data
In half of the cases reported, the suspected drug is clozapine (484 reports). The reports disclose harmful effects on the blood typical of clozapine, such as leucocytopenia, granulocytopenia and agranulocytosis, often with associated signs of infection. The use of clozapine is suspected of having caused 22 fatalities, and in Finland the drug has in fact been under restrictions with regard to use and has been later reintroduced on to the market with new safety instructions. Twelve of the fatalities associated with the use of clozapine are suspected of having been caused by infections due to blood count changes; in five of the cases, increased drug concentrations have been detected.

The second highest number of reports (75) on adverse drug reactions was received regarding chlorpromazine, which has been widely used for a long time; typical harmful effects include symptoms of disordered liver function, e.g. elevated hepatic values, jaundice and hepatitis (22). A total of 17 reports have been received of various blood count changes, and 11 of malignant neuroleptic syndrome. As a result of reports on levomepromazine and promazine, the total number of reports in this group is increased to slightly over 100, but they hardly make any difference to the distribution of adverse reactions.

Risperidone with its 71 reports appears to be the third largest cause for reporting. It is suspected, for example, of having caused hyperprolactinaemia and/or menstrual disturbances (17 cases), malignant neu-
roleptic syndrome (8 cases), delays in the QT interval (5 cases) and blood count changes (4 suspected cases). Typical undesirable effects of antipsychotics also include extrapyramidal symptoms, movement disorders, tremor and increased saliva-
tion which have been reported on 12 occasions.

Olanzapine, having been a slight-
ly shorter time on the market and with its 52 reports, ranks fourth on the list of adverse reactions caused by antipsychotics. Among the variety of symptoms reported, the ma-
jority have been of hyperprolacti-
naemia or milk secretion (6), blood count changes (6), malignant neuro-
roleptic syndrome (6) and various types of oedema (5 reports).

Quetiapine is surpassed by haloperidol, used widely for a long time, with 43 reports, and thiori-
dazine with 39 reports. More than half of the reports on haloperidol (22) were of malignant neuroleptic syndrome, three of tardive dyskine-
sia, three of extrapyramidal symp-
toms and three of various types of arrhythmia, with the rest of the cas-
es figuring as isolated reports. In six of the cases of malignant neuroleptic syndrome, another antipsychotic was also suspected. The use of thiori-
dazine has revealed blood count changes (8 reports), arrhythmia (6) and malignant neuroleptic syndrome (3 reports). Adverse reaction was suspected of having caused six fatal-
ities.

Quetiapine is the most recent ant-
ipsychotic in the market which be-
comes evident in the increased num-
ber of reports (38). The frequency of reporting is usually reduced as cli-
nicians become familiar with the drug and new, 'more interesting' drugs are introduced on to the market. Re-
porting may also be increased by disappointment caused by the new medicinal substances: the expecta-
tions are high, but there is no mira-
cle drug discovered. Eight cases of agranulocytopenia, five cases of neu-
roleptic syndrome, three cases of ar-
rhythmia and a variety of other symptoms have been linked with the use of quetiapine.

The rest of the adverse reactions are spread over several drugs, but yet another prominent place in this group is occupied by lithium with 32 reported cases, six of which refer to a thyroid gland disorder and five involving elevated drug concentra-
tions, three of which were suspected of having been caused by a drug in-
teraction. The dreaded renal effects were suspected in only two cases.

Adverse reactions caused by an-
tipsychotics in 1994–2003
In the past 10 years, 564 reports have been made on the adverse re-
actions caused by antipsychotics. A high proportion of these, i.e. 306 re-
ports, again concerned clozapine and especially the blood count changes caused by it. As the more recent antipsychotics have replaced the use of the older ones, the majority of reports even in this group, af-
ter clozapine, concerned the so-
called "newer antipsychotics". The majority of the reports were firstly of risperidone (65 reports), followed by olanzapine (45 reports) and thirdly, quetiapine (36 reports). Most of these adverse reactions have been discussed above.

Even though the use of newer drugs increased during that period, there were still reports of several se-
rious adverse effects. Hence malig-
nant neuroleptic syndrome was re-
ported on a total of 45 occasions. The majority of the reports con-
cerned clozapine (8 cases), followed by risperidone (8 reports), then sev-
en cases concerning haloperidol, six cases concerning quetiapine and olanzapine, four cases concerning zuclopenthixol, and in isolated cases a few other preparations.

Forty-four reports were made on adverse reactions associated with the heart, as a rule concerning some types of arrhythmia with or without a delayed QT interval.

Clozapine appears in these re-
ports 12 times, risperidone 8, both sertindole and quetiapine 7 and olanzapine five times.

Sertindole is not discussed in de-
tail as it was on the market only for a short time.

The data covering 10 years in-
cludes 32 cases of adverse effects on the blood, mainly agranulocytosis or granulocytopenia, without the in-
volvelement of clozapine. The drugs under suspicion include quetiapine (8 cases), olanzapine (7 reports), risperidone and levomepromazine (4 reports each), as well as some isolat-
ed reports on other drugs.

Reports were made of milk secre-
tion or hyperprolactinaemia on 29
occasions, on 17 of which risperidone was the culprit suspected. Olanzapine was mentioned six times, and both sertindole and quetiapine twice, but clozapine was not mentioned once. In addition to these, risperidone is mentioned in two cases, the symptom being given as amenorrhea.

Liver reactions were reported 28 times with symptoms varying between elevated enzyme levels and severe liver damage. Clozapine appears in this group, too, with 11 reports; chlorpromazine and risperidone are the suspected causes in five cases, olanzapine in four, quetiapine in two cases and chlorprothixene once.

Oedema has been reported on 11 occasions. It is thought to have been caused by olanzapine five times, quetiapine four times, and once each by both risperidone and chlorpromazine.

Extrapyramidal symptoms have been mentioned in the reports on 10 occasions, three of which were associated with risperidone, two with perphenazine and the rest with isolated drugs including, for example, quetiapine from among the more recent drugs.

In the reports involving convulsions (8 cases) clozapine was suspected on three occasions, olanzapine and sertindole twice and risperidone once.

In the cases of tardive dyskinesia, olanzapine, risperidone and sertindole were each suspected as the cause twice, and haloperidol once, a total of seven occasions. Except for one 80-year-old female, the ages of the patients ranged between 21 and 50 years.

A total of 27 deaths have also been reported during the past 10 years. In 10 of the cases a report was made concerning clozapine, but even olanzapine and risperidone were suspected, both on three occasions, albeit risperidone was used in combination. There were isolated reports concerning chlorpromazine (several concomitant drugs), levomepromazine, haloperidol and pro-mazine.

Reports on antipsychotics in 2003
The number of ADR reports totalled 936. Reports on antipsychotics totalled 63. One of the drugs reported again was clozapine (26 reports), whereas quetiapine and risperidone were each the cause for reporting on 14 occasions. Five of the reports on risperidone were associated with the new, intramuscular route of administration. Olanzapine was reported twice.

Antipsychotics and the elderly
The European Medical Evaluation Authority (EMEA) and drug authorities round Europe have issued warnings about the increased risk of cerebrovascular disorders in patients with dementia associated with the use of olanzapine and risperidone. The risk of death in this patient group is also doubled with olanzapine. Cerebrovascular disorders in dementia patients associated with the use of these drugs have not been reported to the Finnish ADR register.

Over the last 10 years, in the group of 65-year-old patients, an antipsychotic agent has been suspected of having played a partial role in causing a patient’s death in six cases, mostly owing to a malignant neuroleptic syndrome. Two of the fatal cases were associated with the use of haloperidol, two with levomepromazine and isolated cases with the combined use of olanzapine and risperidone, haloperidol and chlorprothixene.

Conclusion
About a half of the nearly one thousand ADR reports on antipsychotics concerned clozapine. The introduction of new drugs on to the market is also reflected in the ADR reports made: the new drugs have been reported on frequently. They do not appear to be without adverse effects.