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# Active monitoring of adverse drug reactions in children

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# Research letters

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**An active monitoring system of adverse drug reactions (ADR) in children was developed through a network of family paediatricians. Thè reported incidence of ADRs was 15-1 per 1000 children.**

Few data have been published on adverse drug reactions (ADRs) in children. Although drug metabolism differs in young children and adults, information on effìcacy and toxic effects of drugs is rarely available. Children are not generally included in clinical triais and, therefore, drugs are prescribed based on data derived from triais done in adults. As a consequence, many European children admitted to hospital receive drugs that are prescribed uniicensed or off-label.[1 3] In Italy, spontaneous reporting of ADRs is mandatory. There is, however, a high risk of underestimating thè real incidence of ADRs because of thè lack of data on thè number of drug prescriptions in thè population. To study how an active monitoring system of ADRs in thè paediatric setting couid help in thè collection of information on drug and vaccine safety in children, we developed a network of family paediatricians in northeast Italy.

In March, 1996, thè project was presented to 32 family paediatricians practising in thè Veneto Region, who volunteered to participate. They represented 8% ofall family paediatricians in thè region's health service. 29 agreed to participate in thè study and were trained accordingly.

Each week (from Aprii, 1996 to March, 1997) thè participating paediatricians sent, by modem, a detaiied electronic report of each observed ADR to thè Mattonai Institute of Public Health (Istituto Superiore di Sanità) in Rome, where data were analysed and reported back to thè doctors. To calculate thè incidence of ADRs by prescription, for nine of thè paediatricians in thè Padova province of Veneto, we retrieved from their databases ali prescriptions reimbursable by thè health service issued during thè study period. We calculated incidence per 1000 defìned daily doses of drugs causing ADRs. These doctors observed more than 50% of thè ADRs reported for thè reimbursable prescriptions. Each ADR was assessed according to available information about known drug side-effects—technical reports from pharmaceutical companies and commerciai databases (Micromedex).

About 24 000 children were enrolied on thè lists of thè 29 paediatricians. **We** analysed 244 reports that included 388 events, with a suspected correlation with 266 prescriptions of 73 different substances. 27 doctors

| Age-group (years) | Number of children | Number of ADRs | Incidence per 1000 children | Number of ADRs from vaccines | Incidence per 1000 children |
|---|---|---|---|---|---|
| 0-1 | 469 | 16 | 34-1 | 5 | 10-7 |
| >1-4 | 1825 | 48 | 26-3 | 6 | 3-3 |
| >4-7 | 2086 | 29 | 13-9 | 2 | 0-9 |

| | | | | | |
|---|---|---|---|---|---|
| >7-14 | 3510 | 26 | 7-4 | 1 | 0-3 |

Total **7890 15-1 119 1-8 14**

Table 1: Distribution and incidence of ADRs by age-group

reported at least one adverse event (median 6 [range 1-39]). Thè time distribution of ADRs was quite Constant during thè study, but we saw a slight increase at thè beginning and a decrease at thè end. Thè incidence of ADRs was 15-1 per 1000 children. Incidences by age-group are shown in table 1. Thè drugs most frequently associated with an ADR were cephalosporins and macrolides, whereas penicillins, even with a high number of prescriptions had low incidences (table 2). Two new drugs, licensed in Italy before thè study (nedocromil and cefpodoxime proxetil), led to glossitis, and urticaria and pruritus, respectively. Thè most frequent ADRs were: gastrointestinal (39%), cutaneous (36%), neurological and muscular (4-5%), and haematological (3%) reactions. Ali ADRs were mild and none required hospital admission, although thè study did not have sufficient power to identify rare or serious ADRs.

In Italy, reporting of any ADR to thè Ministry of Health is mandatory for physicians, pharmaceutical companies, pharmacists, and patients. Under-reporting is, however, particularly high compared with other countries. Oniy four ADRs per 100000 children were reported in 1994 and 1995, whereas we calculated an incidence of 15T per 1000 children. An effective active ADR monitoring system is feasible in children. Thè interest shown by thè paediatricians was high and many other doctors asked to join thè group to continue thè project. Proper presentation of thè project and training were cruciai elements in thè involvement of thè

| ADR | DDD | Incidence per | Substances | Type of ADR |
|---|---|---|---|---|
| | | 1000 DDD | | |
| 2 | 28 | 71-43 | Cefpodoxime | Cutaneous |
| 1 | 15 | 66-67 | Calcipotrioì | Cutaneous |
| 1 | 77 | 12-99 | Josamycin | Gastrointestinal |
| 1 | 193 | 5-18 | Cefatrizine | Gastrointestinal |
| 12 | 4373 | 2-74 | Clarithromycin | Cutaneous, gastrointestinal, |
| | | | | eosinophilia |
| 2 | 798 | 2-51 | Ceftibuten | Cutaneous, gastrointestinal |
| 4 | 1969 | 2-36 | Cefuroxime Axetil | Cutaneous, gastrointestinal |
| 4 | 2210 | 1-81 | Azithromycin | Cutaneous, gastrointestinal, |
| | | | | neurological |
| 5 | 3540 | 1-41 | Co-trimoxazole | Cutaneous, neurological |
| 1 | 711 | 1-41 | Ferrous gluconate | Gastrointestinal |
| 5 | 4102 | 1-22 | Erythromycin | Gastrointestinal |
| 21 | 18314 | 1-15 | Amoxicillin plus | Cutaneous, gastrointestinal |
| | | | clavulanic acid | |
| 1 | 915 | 1-09 | Nimesulide | Cutaneous |
| 2 | 1836 | 1-09 | Ketoprofen | Hematuria, hypertranspiration |
| 7 | 6710 | 1-04 | Cefaclor | Cutaneous, gastrointestinal, |
| | | | | neurological |
| 1 | 1165 | 0.86 | Cyproheptadine | Cutaneous |
| 1 | 1292 | 0-77 | Domperidone | Cutaneous |
| 1 | 1380 | 0-72 | Loratadine | Neurological |
| 15 | 27813 | 0-54 | Amoxicillin | Cutaneous, gastrointestinal, |
| | | | | angioedema, fever |
| 4 | 15513 | 0-26 | Salbutamol | Cutaneous, neurological, |
| | | | | cough |
| 1 | 7369 | 0-14 | Nedocromil | Angioedema |

| | | | | |
|---|---|---|---|---|
| 1 | 33114 | 0-03 | Beclometasone | Cough |

**DDD=defined daily doses. Table 2:** ADR incidence by substance

paediatricians. When we compared thè computerised notes with thè cases notifìed to thè coordinating centro, thè reporting was complete. We couid not assess, however, how many ADRs were not reported. This system, therefore, lacks specifìcity and reported ADRs shouid be checked to confìrm thè relation with drug administration. In paediatric wards, most drugs are prescribed off-label,[4] but there are no data on whether this approach is common to primary care. Although in our study no drug was uniicensed or prescribed off-label, our system couid address this issue. Concerns have been raised that with our reporting system many trivial ADRs may be reported, which might make detection of important reactions diffìcult. Continuation ofthe study will givè us information to reassess thè reporting criteria for ali reactions and drugs.

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