Drug-induced agranulocytosis in older people. A case series of 25 patients

SIR—We retrospectively analysed 25 consecutive cases of drug-induced agranulocytosis in older patients in the departments of geriatrics, internal medicine, onco-haematology and rheumatology of the Hôpitaux Universitaires de Strasbourg (a tertiary referral centre), between 1985 and 1997. Patients had to be 70 or older and have unquestionable drug-induced agranulocytosis. All data were obtained from the patients’ files, including medical history, clinical status on referral, relevant bacteriological and biochemical data, blood count and marrow examination (when available). Treatment modalities, use of haematopoietic growth factors, length of time for the neutrophil count to reach >1.5 × 10⁹/l and outcome were also recorded.

The median age was 79 years (range 70–95). The sex-ratio was 1.47, with a predominance of women. A single drug was implicated in 23 cases, whereas the causative agent was unclear in two cases (Table 1).

Twenty-two patients ingested multiple drugs (median 3). A previously normal blood count was not established for all patients before diagnosis, so it is possible that other factors (such as infection) may have caused the agranulocytosis. Diagnosis was made fortuitously in six patients and 19 presented with various symptoms, septicaemia and septic shock being the most frequent. Six patients received haematopoietic growth factors for a mean of 7 days, but their recovery period did not differ from the other patients. The outcome was generally favourable, although two patients, (aged 81 and 90) died of septic shock. A pathogen was found in 40% of cases, which is more frequent than in other series [2, 4]. A bacterial pathogen was found in 40% of cases, which is more frequent than in other series [2, 4]. Antibacterial agents were the agents mainly involved in our series (39%). Although the use of sulphamethoxazole/trimethoprim is discouraged in the UK, it is commonly used in France, despite the fact that physicians are frequently informed of the drug’s toxicity. Our 8% mortality rate is also consistent with other reports: from 3% [3, 5] to 10–20% in other series [4, 6, 7], regardless of age. Several prognostic factors for drug-induced agranulocytosis have been identified; these include age, absolute neutrophil count, percentage of myeloid precursors in bone marrow, presence of septic shock, bacteremia and renal insufficiency [4, 7, 8].

Drug-induced agranulocytosis remains a severe adverse event in older people. Broad-spectrum antibiotics are warranted. The place of haematopoietic growth factors remains to be defined.

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Table 1. Drugs causing agranulocytosis

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug (no. of cases)</th>
</tr>
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<tbody>
<tr>
<td>Anti-inflammatory drugs</td>
<td>Phenylbutazone (1), dapsone (1)</td>
</tr>
<tr>
<td>Anti-aggregating drugs</td>
<td>Ticlopidine (2), acetylsalicylic acid (1)</td>
</tr>
<tr>
<td>Antibacterial agents</td>
<td>Sulphamethoxazole–trimethoprim (3), cefotaxime (1), vancomycin (1), piperacillin (1), imipenem (1), amoxicillin (2)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Mianserin (1), Minaprine (1) Indalpine (2)</td>
</tr>
<tr>
<td>Antithyroid agents</td>
<td>Benzythiouacil (1), carbimazole (2)</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>Captopril (1), Fluvastaine (1)</td>
</tr>
<tr>
<td>Drug not established</td>
<td>Two patients</td>
</tr>
</tbody>
</table>

Letters to the Editor


Do we overlook respiratory symptoms and airflow obstruction in elderly medical admissions?

SIR—Airflow obstruction is often overlooked in elderly subjects living at home [1]. Whether this is also true of acute elderly admissions is not known.

We prospectively studied 100 consecutive patients aged 65 years and above admitted to acute general medical wards at a district general hospital. We excluded patients who were known to have chronic obstructive airways disease and those unable to perform spirometry. Within 5 days of admission, we asked subjects to complete a respiratory questionnaire previously used in epidemiological studies of respiratory disease in older people [2]. We performed spirometry on all patients. If airflow obstruction was present (the ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) was <60% and the FEV1 <80% predicted), we repeated measurements after 200 mg salbutamol inhaled via a large volume spacer device. Reversibility was taken to be >15% improvement in FEV1 with a 200 ml increase in FEV1 [3]. If patients had no reversibility to salbutamol, we repeated spirometry after 40 μg ipratropium bromide.

Of 100 patients, 54 were excluded (22 had known chronic obstructive airways disease, 32 were unable to perform spirometry). Of 46 patients not known to have chronic airflow obstruction (mean age 80 years, range 65–93), 35 (76%) reported any respiratory symptom. Twelve (26%) patients had airflow obstruction, of whom five (42%) demonstrated reversibility to bronchodilators. At least one respiratory symptom was reported by all 12 patients with undiagnosed airflow obstruction and by 23 of 34 (68%) patients without airflow obstruction.

Respiratory symptoms and airflow obstruction in older people admitted to hospital are common and frequently overlooked. Respiratory symptoms have low specificity for respiratory disease in older people [4]. Studies are currently underway to address whether patients with undiagnosed chronic airflow obstruction derive benefit from treatment. We would recommend objective lung function assessment with spirometry for elderly patients with respiratory symptoms.

Rectal examinations in elderly subjects

SIR—I read with interest Morgan and co-workers’ article on patients’ and doctors’ attitudes to rectal examination in elderly subjects [1]. This excellent article should finally put to rest the fallacy that digital rectal examination (DRE) is not performed because of patient preference.

Similar attitudes were found in a slightly younger group of patients involved in a study of early detection of prostate cancer [2]. The mean age of men with prostate cancer was 65 years, 9 months, range 55–78. In 2057 asymptomatic men investigated by DRE, 64 men (3.1% of those screened) were discovered to have colorectal or prostate cancer. None refused a DRE. This reiterates the acceptability of DRE and the fact that it should be included in every clinical examination as, if malignancy is diagnosed, curative or palliative therapy can be commenced.

Training is the important issue. Morgan et al. reported that 65% of doctors in their study did not feel they had received sufficient training at DRE. Good training at DRE is becoming increasingly difficult due to increasing awareness of the ethical issues of consent [3]. As training in an ordered systematic approach has been shown to allow a generalist to achieve a similar accuracy to a specialist [4], the procedure needs to be actively taught and encouraged by senior staff to allow junior staff to gain adequate experience and confidence in this important area of clinical examination.

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Letters to the Editor

SIR—We read with interest the review of Agrell and Dehlin on the clock-drawing test [1]. The authors discussed the feasibility, sensitivity and specificity for measuring cognitive dysfunction and dementia using several scoring systems. Unfortunately, there was no discussion of inter-rater reliability, an important feature of diagnostic tests [2]. Most studies cited did report on inter-rater reliability.

There are different measures for inter-rater reliability which can complicate comparisons by reviewers and researchers who can reach different conclusions about inter-rater reliability of a test depending on the measures used. To illustrate this, we re-investigated the inter-rater reliability of two frequently used scoring methods of the clock-drawing test [3, 4].

The clock drawings of 120 consecutively referred patients were used in the outpatient memory clinic of the Academic Hospital, Nijmegen. Two raters scored independently and were blinded for the diagnostic outcome of the clock drawings according to the methods of Sunderland and Watson [3, 4]. Sunderland proposed a 10-point scoring method, in which 10 points reflect a perfect clock and lower scores reflect minor to major cognitive impairment. Watson proposed an ‘objective’ method, in which the rater judges whether each of the quadrant holds three numbers. Scores range from 0 (perfect score) to 7 (worst score).

The inter-rater agreement was expressed as the Pearson correlation was 0.88 (original article 0.90 < P < 0.93)—which is still quite high (original article 0.86 < r < 0.97). For Watson’s method, the χ was 0.3 (which is fair), while the Pearson correlation was 0.62 (P < 0.000)—which is still quite high (original article 0.90 < r < 0.95).

We were not able to reproduce the good correlation of the Watson method as reported in the original publication. This questions whether the Watson method is as objective as the authors stated. Nevertheless, a lower correlation might be explained because we used a free-drawn instead of a pre-drawn circle.

In conclusion, the inter-rater reliability of scoring methods of the clock-drawing test is important. Comparison of inter-rater reliability can be difficult because different measures are used. The inter-rater reliability can be overestimated when expressed as correlation coefficients rather than χ scores.

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References


Authors’ reply

SIR—We appreciate the comments made by Drs van Hout and Berkhout on our review of the clock-drawing test [1]. Inter-rater reliability is indeed important. We present the inter-rater reliability of the scoring systems which we presented in our overview (Table 1).

Table 1. Inter-rater reliability of the scoring systems presented in the overview

<table>
<thead>
<tr>
<th>Reference</th>
<th>Inter-rater reliability (r)</th>
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<tbody>
<tr>
<td>Sunderland et al., 1989</td>
<td>0.86–0.97</td>
</tr>
<tr>
<td>Mendez et al., 1992</td>
<td>0.94</td>
</tr>
<tr>
<td>Watson et al., 1993</td>
<td>0.85–0.95 (Spearman’s)</td>
</tr>
<tr>
<td>Forstl et al., 1993</td>
<td>0.78 (Pearson’s)</td>
</tr>
<tr>
<td>Taikkio et al., 1992</td>
<td>0.90–0.95</td>
</tr>
<tr>
<td>Manos and Wu, 1994</td>
<td>0.88–0.96 (Spearman’s); 0.88–0.97 (Pearson’s)</td>
</tr>
<tr>
<td>Ishii et al., 1993</td>
<td>NR</td>
</tr>
<tr>
<td>Shau-Haim et al., 1996</td>
<td>NR</td>
</tr>
<tr>
<td>Shulman et al., 1986</td>
<td>NR</td>
</tr>
<tr>
<td>Wolf-Klein et al., 1989</td>
<td>NR</td>
</tr>
<tr>
<td>Friedman, 1991</td>
<td>NR</td>
</tr>
<tr>
<td>Death et al., 1993</td>
<td>NR</td>
</tr>
<tr>
<td>Halligan et al., 1989</td>
<td>NR</td>
</tr>
<tr>
<td>Schenkenberg et al., 1980</td>
<td>NR</td>
</tr>
<tr>
<td>Kokmen et al., 1991</td>
<td>NR</td>
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</table>

NR, not reported.
Watson et al., 1993: Spearman’s r for two physicians 0.93; for two nurses 0.90; for a physician and a nurse 0.88–0.95.

Letters to the Editor

Ainslie and Murden, in their study of poorly-educated people [2], scored the clock-drawing test according to Shulman et al. [3], Sunderland et al. [4] and Wolf-Klein et al. [5]. They found a k value of 0.74 for Shulman et al., 0.73 for Wolf-Klein et al. and 0.48 for Sunderland et al.

Inter-rater reliability is often presented in different ways: as Pearson’s correlation coefficient (assuming an approximately normal distribution), as Spearman’s r (rank correlation) or simply as r and as k, which probably is the best statistical method in context [6].

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Heart failure: a diagnostic and therapeutic dilemma in elderly patients

SIR—Gillespie et al. have written an excellent review [1]. However, I would like to make the following comments.

About half of acute myocardial infarction survivors develop heart failure. There is controversy about the use of aspirin in heart failure. The benefit of aspirin in myocardial infarction was established in the ISIS-II trial. The benefits of aspirin on chronic coronary artery disease are less certain. Aspirin allegedly attenuates the haemodynamic effects of angiotensin converting enzyme (ACE) inhibitors. Several ACE inhibitor trials (AIRE, CONSENSUS and SOLVD) have demonstrated reduced benefits in patients taking aspirin. There was no reduction of benefit in the SAVE and TRACE trials, whereas both the AIMIS and PARIS trials suggested increased mortality of patients with heart failure on aspirin.

The relation between warfarin use and survival and cardiovascular mortality was assessed in the patients enrolled in the SOLVD study which added to circumstantial evidence to support the use of antithrombotic therapy (particularly warfarin) in patients with heart failure or a low ejection fraction (≤ 5%). A prospective, randomized trial is required to answer this important question definitively [2].

Between 30 and 50% of patients with heart failure died from a rhythm disturbance in the SOLVD/V-HeFT II trials. The EMIA trial showed that amiodarone reduced arrhythmic death—but not all-cause mortality or cardiac mortality in survivors of a myocardial infarction with left ventricular dysfunction (left ventricular ejection fraction ≤ 40%) [5]. Physicians must weigh the adverse effects of amiodarone against any benefit. The evidence does not justify the routine use of amiodarone in survivors of myocardial infarction who have left ventricular dysfunction.

Could implantation of an automatic cardiac defibrillator prevent sudden death in heart failure? Three studies (AIVD, CIDS and CASH) showed a mortality reduction of 20–40% in patients with the defibrillator compared with the best anti-arrhythmic drug therapy (Amiodarone). We cannot yet identify patients at high risk of arrhythmic death whose competing risk of death from heart failure is sufficiently low so that the benefit conferred by the implanted defibrillation could improve overall mortality [4]. In patients with heart failure refractory to conventional oral medication, the intermittent use of monitored intravenous infusions of dobutamine helps selected patients and minimizes the development of tolerance [5].

Heart failure: a diagnostic and therapeutic dilemma in elderly patients

SIR—Dr Kausar raises some important points which require clarification.

The merits of warfarin in patients with heart failure who are in sinus rhythm are unclear [1]. However, in patients with atrial fibrillation, the advantages of warfarin over aspirin are well established in the...
Letters to the Editor

Driving safety: motivating messages

SIR—Physicians often have opportunities to encourage patients’ safe behaviours [1]. Driving accident rates are highest among young (<25 years) and senior (>55 years) drivers [2]. Older drivers reportedly use seatbelts less often [3] and equivalent crashes lead to greater physical injuries [4]. Therefore, it is important to encourage seatbelt use. Knowing how optimally to motivate this is important.

Quillian [5] reported different motivations when deciding not to drive while intoxicated. Younger drivers were unwilling to drive because of legal consequences and senior drivers because of fear of physical injury.

We report two observations confirming that older drivers are more motivated by concerns of physical injury and younger drivers more motivated by legal consequences. Fifteen college students (mean age = 20.1 years) and 15 seniors (mean age = 68.7 years) were shown two pairs of signs emphasizing the need to buckle seatbelts to avoid either legal or physical consequences. One pair read “buckle up (picture of policeman) avoid tickets” and “buckle up (picture of surgeon) avoid hospitals”. The second pair read “buckle up (picture of a judge) avoid arrest” and “buckle up (picture of a stretcher) avoid injury”. Participants selected which sign in each pair was more likely to encourage them to fasten their seatbelts. College students predominantly selected signs emphasizing legal over physical consequences (76% versus 24%), while seniors made the opposite selection (18% versus 82%, $\chi^2 = 5.23, P = 0.02$).

Next, we made signs measuring 3 × 2 feet which incorporated the ‘avoid tickets’ and the ‘avoid hospitals’ messages. Investigators sat at two stop-signs, near a retirement village and a college campus and estimated drivers’ ages, then recorded whether the driver was using a seatbelt or fastened it. Sixty-six unbelted drivers, <25 years or >55 years, passed during three conditions: (i) when a sign was placed next to the stop-sign emphasizing legal over physical consequences (76% versus 24%), (ii) when the sign emphasized physical consequences, (iii) with no sign.

No-one fastened the belt when no sign was posted. Young drivers did so 9% versus 46% of the time with the ‘physical’ versus ‘legal’ signs, while seniors did the opposite. Fastening belts 70% versus 36% of the times ($\chi^2 = 4.00, P = 0.045$). This confirms that seniors are motivated to change behaviour by concerns about physical injury, while younger drivers are more influenced by considerations of legal repercussions. This may have implications for how physicians advise older and younger patients on driving safety.

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Letters to the Editor

