METAMIZOLE (DIPYRONE) AND AGRANULOCYTOSIS IN GERMANY: LONGTERM CONSEQUENCES OF A REGULATORY MEASURE IN 1986

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Background

In 1986 risk of agranulocytosis and shock in association with metamizole prompted regulatory measures in Germany. Over-the-counter availability was abandoned. All fixed-combinations were withdrawn from the market. Indications were restricted to acute post-traumatic and post-surgical pain, colic and cancer pain, and treatment of pain or fever if other measures are not indicated or failed. After an initial decline, prescriptions increased from < 20 million defined daily doses in 1990 to > 114 million in 2009 (1). Concurrently spontaneous reports of agranulocytosis increased from about 10 per year in 1990 to > 30 in 2009 (Fig. 1).

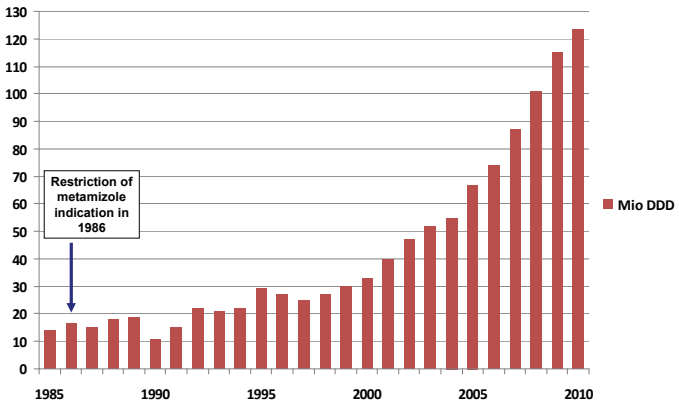

Figure 1: Prescriptions [million defined daily doses (DDD)] of metamizole reimbursed by German Statutory Health Insurance.

Objective

To assess reports of agranulocytosis in association with metamizole with regard to indication, severity and outcome.

Methods

Reports of suspected metamizole-induced agranulocytosis between 1990 and 2010 were identified in the German spontaneous reporting database by a standardised MedDRA-Query (SMQ agranulocytosis). Reports initially received by the DCGMA were eligible for assessment since original reporting forms and additional documents are available (Fig. 2).

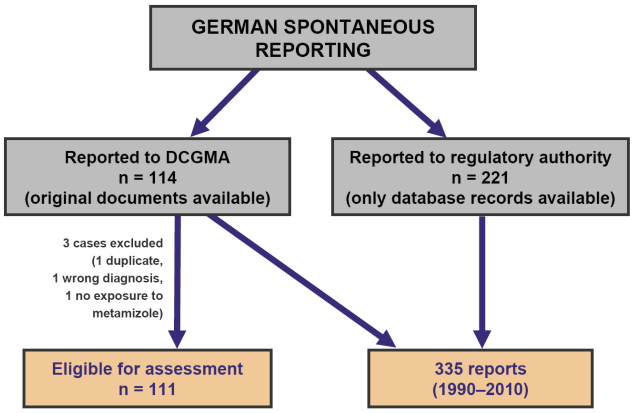

Figure 2: Identification and enrollment of eligible case reports of agranulocytosis in association with metamizole in the German spontaneous reporting system.

Results

A total of 335 reports were identified of which 114 were eligible for assessment. 3 cases were excluded (wrong diagnosis (2x), missing exposure to metamizole (1x)). 111 reports were assessed in detail. Patient characteristics are presented in table 1, median time to onset in figure 4. The most frequent indications for metamizole were post-traumatic and post-surgical pain (32 cases, 28.8 %), while cancer pain (5, 4.5 %) and colic (none) were of minor relevance (Fig. 5). In roughly half of the cases prescription of metamizole was not clearly in conformity with the approved indications.

Table 1: Patient characteristics.

Total number of cases	**111**
Number of females	71 (64 %)
Mean age [years]	61.1 (range 11–93)
Additional information available (e. g. referral letters or post-mortems)	68 (61 %)
Bone marrow sample	37 (33.3 %)
Prescription during hospitalisation	55 (49.5 %)
Self-medication	4 (3.6 %)
Pancytopenia (without infectious complication reported)	13 (11.7 %)
Aplastic anemia suspected	5 (4.5 %)
Infectious complications	67 (60.4 %)
Median days to onset of agranulocytosis	10 (range 1–150)
Fatal outcome	30 (27 %)
Intensive care (non-fatal outcome)	11 (9.9 %)

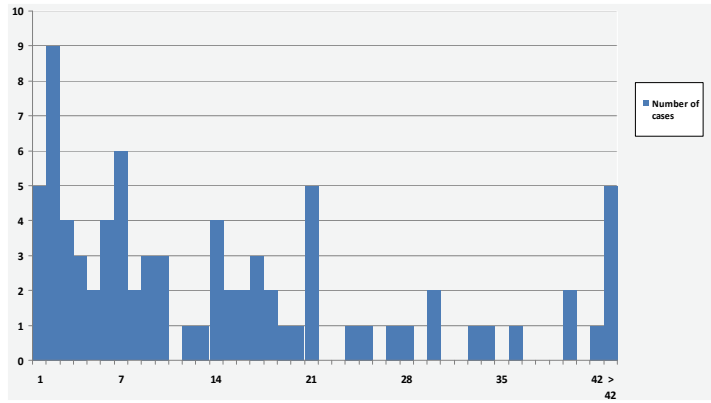

Figure 4: Interval [days] from beginning of medication with metamizole until diagnosis of agranulocytosis (data available for 80 of 111 cases (72.1 %)).

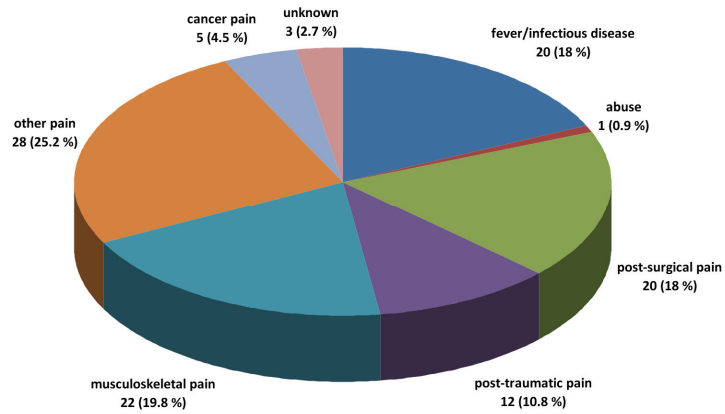

Figure 5: Indications for metamizole.

Conclusion

Although agranulocytosis is a very rare adverse reaction of metamizole the number of reports in consequence of the increase of prescriptions and the severity of the cases indicate a serious health problem. The proportion of female patients, fatal outcome and median time to onset in our cases are in line with findings in Sweden (2). The prescribing pattern shows that physicians may be unaware to some extent of the restricted indications of metamizole. Therefore, the German Federal Institute for Drugs and Medical Devices (BfArM) and the DCGMA notified healthcare professionals about the risk of agranulocytosis in association with metamizole and the approved indications by three publications in March 2009, August and September 2011.

References

1. Schwabe U, Paffrath D (Editors): Arzneiverordnungs-Report (German Drug Report) 2011. Berlin, Heidelberg: Springer Medizin Verlag, 2011.
2. Hedenmalm K, Spigset O: Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). Eur J Clin Pharmacol 2002; 58: 265-274.