

Fatal drug-induced interstitial pneumonitis associated with toxic drug-drug interactions of amitriptylin and clozapine.

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Introduction

Drug-induced pulmonary toxicity is a still growing and often underestimated clinical problem. Often the connection with drug-use and the development of related inflammatory damage or idiosyncratic toxicities is hard to recognize and objectify, especially in those patients using multiple drugs. We describe a case of interstitial pneumonitis secondary to drug toxicity associated with a combination of amitriptyline and clozapine.

Case report

A 65-year-old female with a history of schizophrenia was admitted because of a humerus fracture. Her daily medication (Table 1) consisted among others of amitriptyline (250 mg/day) and clozapine (300 mg/day). Surgery was performed, 11 days later she was admitted to the intensive care unit because of respiratory failure. Computed thorax tomography showed diffuse interstitial pneumonia with ground glass opacity. (Figure 1) Bronchoalveolar lavage fluid showed signs of inflammation with an increased number of neutrophils (65 %) and lymphocytes (21 %), without any signs of infection (intracellular microorganisms 0%; Iron, Gram, and Grocott staining all negative). Also, the patient possessed a fully functional cytochrome P450 (CYP) 2D6 enzyme. According to these findings, drug-induced pulmonary toxicity was suspected. Serum concentrations of amitriptyline and clozapine were 850 µg/L (therapeutic range: 100-250 µg/L) and 2657 µg/L (therapeutic range 350-1000 µg/L) respectively. Both drugs were stopped immediately and high dose corticosteroids and N-acetylcysteine started, but outcome was nevertheless inevitable.

Discussion and Conclusion

The use of various drugs metabolized by the same enzymatic pathway may result in significant accumulation of these drugs, leading to toxic serum levels and possible severe side effects, even in subjects with functional CYP enzymes. In this case drug-drug interactions (Table 1 and 2) led to toxic serum concentrations of amitriptyline and clozapine and finally resulted in fatal drug-induced pulmonary toxicity.

Figure 1: CT Thorax: Diffuse interstitial pneumonia with predominantly ground glass opacity.

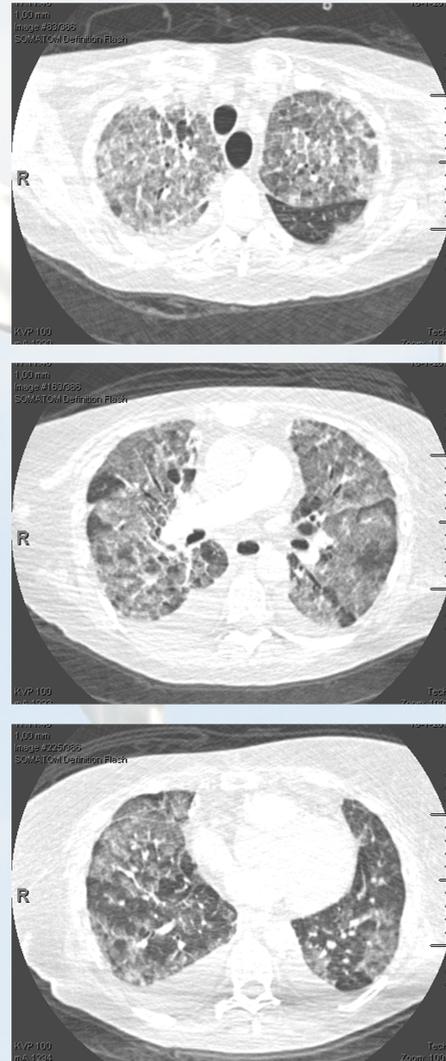


Table 1: Drug-drug interactions in home medication regime.

Affected Drug	Change	Causative agent
Amitriptylin	Some	Clozapine, Promethazin
Clozapine	Some	Clozapine, Amitriptylin
Promethazin	Some	Promethazin, Amitriptylin
Acetaminophen	No	

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Table 2: Drug-drug interactions in hospital medication regime.

Affected Drug	Change	Causative agent
Amitriptylin	Major	Clozapine, Promethazin, tramadol, tramadol's metabolite, midazolam, pantoprazole, lorazepam, diclofenac, salbutamol
Clozapine	Major	Promethazin, lorazepam, pantoprazole, amitriptylin
Lorazepam	Major	Promethazin, clozapine, diclofenac, Amitriptylin
Promethazin	Some	clozapine, amitriptylin
Diclofenac	Some	Furosemide, amitriptylin, midazolam, promethazin, pantoprazole, clozapine, tramadol's metabolite, acetaminophen, lorazepam
Tramadol prodrug	Some	Promethazin, diclofenac, clozapine, midazolam, amitriptylin
Midazolam	Some	Promethazin, pantoprazole, lorazepam, diclofenac, amitriptylin
Heparin	Some	Diclofenac
Furosemide	Some	Diclofenac, salbutamol, acetaminophen
Salbutamol	Some	Amitriptylin, clozapine, furosemide
Ipratropium bromide	No	
Pantoprazole	No	
Acetaminophen	No	
Tramadol's active metabolite	No	

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