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Safe drugs to fight mutant protein overload and alpha-1-antitrypsin deficiency

To the Editor:

We read with interest the commentary, "Drug enhanced autophagy to fight mutant protein overload", by Mehrpour and Codogno [1]. The authors discuss recent experimental findings by Hidvegi *et al.*, in a *in vitro* and in an animal model of alpha-1-antitrypsin (AT) deficiency, which raise the interesting possibility that the iminostilbene derivative carbamazepine (CBZ) could be used to treat this severe liver disease in humans [1,2]. The authors correctly conclude that these findings have provided the rationale for studies on CBZ in patients with AT deficiency [1]. However, in our opinion, they overlooked that at least one crucial, open question remains to be clarified, before application of these findings in clinical practice. This concerns the fact that in the preclinical mouse model of AT deficiency, used for evaluating the CBZ effects, the results have been obtained with doses of the drug significantly higher than the doses used in humans (200 mg/kg/day *vs.* 10–20 mg/kg/day), lower doses of CBZ have not been effective, and in the study, the plasma levels of CBZ have not been evaluated [1,2]. However, it is worth noting that as stated by Hidvegi *et al.* in the discussion section of their paper [2], "Effective doses of drugs can be 10- to 20-fold higher in mice because of the higher ratio of surface area to weight when compared to humans", and that the findings from preclinical and clinical studies exemplified in Table 1 fit this statement.

CBZ is a safe drug with a wide clinical spectrum of action which ranges from epileptic seizures to cerebellar tremors and myotonia [3–5], with well-known plasma therapeutic levels in each of these pathologies [3–5]. In particular, an analysis of the relationship between CBZ doses per body weight, necessary for clinical effects and CBZ plasma levels, indicates that in humans severe neurological and cardiovascular effects are usually seen at CBZ daily doses higher than 20 mg/kg, and at plasma CBZ levels greater than 12 μg/ml [6,7].

Oral doses and plasma therapeutic levels of CBZ in preclinical and clinical studies are shown in Table 1. In preclinical studies, oral doses of CBZ seem poor predictive of plasma concentrations of the drug, likely due to the very different bioavailability of oral CBZ preparations used in the different studies. Thus, in preclinical studies, the determination of plasma CBZ concentrations seems particularly advisable. In clinical studies, instead, some relationship between oral doses of CBZ and therapeutic plasma levels seems evident.

At present, the determination of plasma CBZ levels is a routinary and rather easy task both in clinical and experimental settings [3–5], and further studies on the therapeutic plasma levels of CBZ in preclinical animal models of AT deficiency could help to improve the quality of clinical trials aimed at assessing the efficacy of CBZ in patients with liver disease as a result of AT deficiency.

Moreover, another relevant question the authors discussed in the commentary is that the findings by Hidvegi *et al.* also provide a proof of principle for therapeutic use of other safe autophagy enhancer drugs, potentially useful to fight protein overload in different genetic diseases [1]. Interestingly, the β-lactam antibiotic ceftriaxone, commonly used for decades in patients with moderate to severe exacerbations of chronic obstructive pulmonary disease related to AT deficiency [8], was recently shown to also be able to eliminate the toxic effects of misfolded glial fibrillary acidic protein (GFAP) in a cellular model of Alexander disease, a rare, usually fatal neurodegenerative disorder, by decreasing GFAP intracytoplasmic aggregates, through complex biochemical mechanisms involving GFAP promoter down-regulation and enhancement of autophagy [9,10]. The question is now whether ceftriaxone will also be useful in treating other diseases caused by intracellular accumulation and aggregation of misfolded proteins such as AT deficiency.

Table 1
Oral doses and plasma therapeutic levels of carbamazepine in preclinical and clinical studies.

Preclinical studies in mice (22-35 g):	Oral doses	Plasma concentrations (μg/ml)	References
After 0.5-1 h, single oral administration			
Mice with KA acute seizures	0.5 mg/kg	10.1 ± 5.2 (M ± S.D.)	Nishimura *et al.*, 2008 Biol Pharm Bull 31;2302
Mice after MES test	50 mg/kg	8.1 ± 0.6 (M ± S.E.)	Masuda *et al.*, 1979 Epilepsia 20;623.
After chronic exposure, 5-6 weeks			
Mice with megalencephaly and partial seizures	500 mg/kg/day	1.2-6.2	Almgren *et al.*, 2008 Neurobiol Dis 32;364
Mice after MES test	407 ± 13 mg/kg/day	12 ± 1.7 (M ± S.E.)	Christensen *et al.*, 2004 Am J Obst Gynecol 190;293
Clinical studies			
Focal and generalized tonic-clonic seizures	10-20 mg/kg	4-12	Cereghino *et al.*, 1974 Neurology 24;357
Trigeminal neuralgia	200-1400 mg/day	5.7-10.1	Tomson *et al.*, 1980 Arch Neurol 37;699
Myotonia	600-800 mg/day	1.2-9.9	Sechi *et al.*, 1983 Eur Neurol 22;113
Cerebellar tremors	400-600 mg/day	6-9.6	Sechi *et al.*, 1989 Neurology 39;1113
Paroxysmal kinesigenic choreoathetosis	100-200 mg/day	1.75-4.5	Wein *et al.*, 1996 Neurology 47;1104
Acute mania	400-2000 mg/day	4-15	Spina, Perugi, 2004 Epileptic Disord 6;57

KA, kainic acid-induced; M ± S.D., mean ± standard deviation; MES, maximal electroshock seizure; M ± S.E., mean ± standard error.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Mehrpour M, Codogno P. Drug enhanced autophagy to fight mutant protein overload. J Hepatol 2011;54:1066–1068.
[2] Hidvegi T, Ewing M, Hale P, Dippold C, Beckett C, Kemp C, et al. An autophagy-enhancing drug promotes degradation of mutant alpha1-antitrypsin Z and reduces hepatic fibrosis. Science 2010;329: 229–232.
[3] Cereghino JJ, Brock JT, Van Meter JC Penry JK, Smith LD, White BG. Carbamazepine for epilepsy. A controlled prospective evaluation. Neurology 1974;24:401–410.
[4] Sechi GP, Zuddas M, Piredda M, Agnetti V, Sau G, Piras ML, et al. Treatment of cerebellar tremors with carbamazepine: a controlled trial with long-term follow-up. Neurology 1989;39:1113–1115.
[5] Sechi GP, Traccis S, Durelli L, Monaco F, Mutani R. Carbamazepine versus diphenylhydantoin in the treatment of myotonia. Eur Neurol 1983;22:113–118.
[6] Holmes GL. Carbamazepine. Adverse effects. In: Levy RH, Mattson RH, Meldrum BS, Perucca E, editors. Antiepileptic drugs. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 285–297.
[7] Tibbals J. Acute toxic reaction to carbamazepine: clinical effects and serum concentrations. J Pediatr 1992;121:295–299.
[8] Hunter MH, King DE. COPD: management of acute exacerbations and chronic stable disease. Am Fam Physician 2001;64:603–613.
[9] Bachetti T, Di Zanni E, Balbi P, Bocca P, Prigione I, Deiana GA, et al. In vitro treatments with ceftriaxone promote elimination of mutant glial fibrillary acidic protein and transcription down-regulation. Exp Cell Res 2010;316:2152–2165.
[10] Sechi GP, Matta M, Deiana GA, Balbi P, Bachetti T, Di Zanni E, et al. Ceftriaxone has a therapeutic role in Alexander disease. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:416–417.

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Recombinant factor VIIa to treat severe bleeding in patients with liver disease: Pitfalls and possibilities

To the Editor:

Patients with liver disease frequently develop substantial changes in their hemostatic system [1]. Recent laboratory and clinical data are compatible with the concept of rebalanced hemostasis in liver disease [2]. According to this concept, the average patient with liver disease is in hemostatic balance due to a concomitant decrease in pro- and anticoagulant pathways. The hemostatic balance in patients with liver disease, however, is much more fragile as compared to the hemostatic balance in healthy individuals. Consequently, patients with liver disease are at risk for both bleeding and thrombosis when the balance is disturbed. Unfortunately, there is currently no clinical or laboratory test able to predict whether a patient with liver disease is at risk for either bleeding or thrombosis.

In a recent commentary in the section "International Hepatology" of this *Journal*, Thabut and coworkers address the question whether administration of recombinant factor VIIa (NovoSeven, rFVIIa) to patients with liver disease poses them at an increased risk for thrombotic complications [3]. The authors conclude that the use of rFVIIa to patients with uncontrollable bleeding may be justified, and potential thrombotic events should be considered as 'collateral damage'. Here, we aim to comment on the use of rFVIIa in patients with liver disease to better appreciate the risk-benefit ratio in different clinical scenarios.

Current clinical data do not support prophylactic administration of rFVIIa to prevent excessive bleeding during surgical procedures including partial hepatectomy and liver transplantation [4,5]. Also, administration of rFVIIa to patients with variceal bleeding is not indicated based on randomized controlled trials.

Although the average patient with liver disease is in hemostatic balance, there are situations in which severe and uncontrollable bleeding does occur [1]. If the primary cause of bleeding is not surgical and not primarily related to (excessive) portal hypertension, administration of rFVIIa may be beneficial, which is supported by anecdotal reports [6,7]. The main advantage of rFVIIa over other hemostatic therapies, such as blood product infusion, is the low volume, which prevents fluid overload and exacerbation of portal hypertension. In addition, transfusion-related complications such as transfusion-related acute lung injury and other transfusion reactions do not occur when rFVIIa is administered.

The theoretical advantages of rFVIIa when used as a "rescue agent" need to be balanced against a potentially increased risk of thrombosis. We believe that clinical studies are required to establish whether rFVIIa is truly effective in controlling bleeding complications in patients with liver disease. Furthermore, we believe it is important to realise which types of uncontrollable bleeding might benefit from rFVIIa administration, and in which cases therapy with rFVIIa is likely futile.

The patients with uncontrollable bleeding that may benefit from rFVIIa are those patients in whom the bleeding complication is likely a result of an inadequate coagulation system. Examples of this are patients with massive hematomas, patients with bleeding complications after small invasive procedures including dental extraction, liver biopsy, paracenthesis and thoracenthesis, and patients with bleeding complications during or after larger invasive procedures. In the latter case, it should be excluded that there is a surgical cause for the bleeding complication. Clinically,