Treatment of fatigue in Hepatogastroenterology: fact or fiction?

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Although fatigue is the most common complaints reported by patients in primary care [1], last decades of research have been hampered by the lack of an objective measurement of the subjective experience of fatigue. The Fatigue Impact Scale (FIS) questionnaire was developed in 1994 by Fisk and colleagues to quantify the specific impact of fatigue on quality of life [2]. In Hepatogastroenterology, this validated tool has confirmed the disabling effect of fatigue in many chronic illness such as chronic hepatitis C [3, 4] and primary biliary cirrhosis [5, 6] but also in functional bowel disorders namely the irritable bowel syndrome (personal data). For instance, the FIS questionnaire is of particular interest in ongoing trials aimed at reducing fatigue. Considering the high prevalence of fatigue, thus inducing a considerable burden to the health care system, the elucidation of its still poorly known pathogenesis and the development of effective therapies for its relief are important goals for research in Hepatogastroenterology.

Physiopathology

Ten years ago, Swain and Maric [7] have proposed three theories based on findings in a rat model, that considered central incompetence or variations thereof as a critical issue in the pathogenesis of fatigue: (i) neuroendocrine causes, with abnormal function of the hypothalamic-pituitary-adrenal axis; (ii) alterations in immune activation and cytokines release (e.g. proinflammatory cytokines); and (iii) abnormalities in neurotransmission, particularly in the central serotonin pathway. Whether the disturbances of the hypothalamic-pituitary-adrenal axis observed by some authors, but not all, are of functional importance remain controversial (for review [8]). To date, there is growing evidence that the central component of fatigue associated with chronic conditions plays a key role compared to peripheral mechanisms. Subsequent studies in animals and humans have confirmed the importance of alterations within the brain stem, in the chronic fatigue syndrome [9, 10], cholestatic liver diseases [11] or chronic hepatitis C [12, 13]. The recognition of altered neurotransmission has also brought the possibility of pharmacological manipulation of receptors and transmitters, especially serotonin (5-HT), opioid, and substance P (e.g. substances that can influence behavior in both animals and humans). Moreover, the key role of immunity has recently been enlightened and high circulating leptin and TNF-α (i.e. proinflammatory cytokines) levels have been associated with the severity of fatigue in patients with chronic hepatitis C [3] or irritable bowel syndrome (personal data). Nevertheless, the pathogenesis of fatigue probably does not lend itself to this reductionist thinking and given the many confounding factors that may impinge on behavior, it is likely that fatigue is mediated through a more complex dysfunction of the central nervous system, neurotransmission, immunity, endocrine factors and micronutrients which may be altered at various degrees depending of the underlying disease.

What are the ways to improve fatigue in GI diseases?

Selective serotonin reuptake inhibitors and 5-HT receptor antagonists

Considering the altered neurotransmission, it is well established that the serotonin pathway is involved in both anxiety and depression and may participate to fatigue. Therefore, the drug class of selective serotonin reuptake inhibitors and 5-HT receptor antagonists have been evaluated to treat fatigue in many conditions with conflicting results. In an open study, it was shown that blockade of both 5HT2 and HT3 receptors with mirtazapine was associated with a 40 % or more reduced intensity of fibromyalgia symptoms, including fatigue, as well as reduced severity of depression [14]. In another study, fatigue was significantly and substantially reduced when patients with chronic fatigue were switched from placebo to 20 or 40 mg of the serotonin reuptake inhibitor citalopram [15]. However, the findings were less impressive in a design comparing the effect of citalopram and placebo after two months of treatment [15]. In patients with chronic fatigue, the oral administration of the 5-HT2 receptor antagonist ondansetron has also been shown to relieve fatigue [16]. Conversely, fatigue was not improved in a large cohort of 549 fatigue patients with cancer receiving chemotherapy who were randomly assigned to receive either 20 mg of oral selective serotonin reuptake inhibitor paroxetine hydrochloride daily or placebo for 8 weeks [17]. In chronic liver diseases, there is growing acceptance that cholestasis is associated with altered opioid and 5-HT mediated neuromodulation, which contributes to the pruritus of cholestasis [11]. It is noteworthy that 5-HT, like opioid agonists, modulates nociception in normal rats [18], and might also interfere with the perception of pruritus. This concept...
is supported by the fact that the intravenous administration of the selective 5-HT\textsubscript{3} receptor antagonist ondansetron to patients with cholestatic liver diseases has been associated with acute improvement of pruritus [19]. Therefore, this drug class (e.g. serotonin reuptake inhibitors and 5-HT receptors antagonists) was used in several trials aimed at reducing fatigue associated with cholestasis. In a rat model, Swain et al. [20] have recently demonstrated that cholestasis was associated with increased central 5-HT\textsubscript{3} receptor expression in a brain area implicated in behavioral activation. Moreover, in the same model, inhibition of 5-HT\textsubscript{3} receptor activation was shown to improved cholestasis associated fatigue-like behavior [20]. In alcoholic dependant individuals, the selective 5-HT\textsubscript{3} receptor antagonist ondansetron (16 µg/kg twice daily) has been shown to have a greater thera-peutic efficacy at alleviating symptoms of overall mood disturbance, fatigue, vigor, confusion/bewilderment, and depression among early onset alcoholics compared with late-onset alcoholics [21]. Finally, a woman with chronic hepatitis C and profound fatigue has been reported to become symptom free when treated with long-term ondansetron 4 mg twice daily [22]. In the light of these findings, we were encouraged to perform a double blind randomized trial with this compound in a cohort of 36 patients with chronic hepatitis C and fatigue. In this study, patients did not received any antiviral therapy and one month oral administra-
tion of the 5-HT receptor type 3 antagonist ondansetron (4 mg twice daily) induced a significant 30\% improvement of the total score of fatigue measured with the FIS whereas placebo did not. Interestingly, this effect persisted one month after the treatment had been stopped [23]. In this study, ondansetron was also effect-
tive in diminishing the scores of the Beck Depression Inventory used to measure depression. Although the mechanism of this effect remains unclear, we have observed that circulating leptin levels were reduced in the group of patients receiving ondanset-
ron but not in the placebo group (unpublished data). Further tri-
als are warranted to confirm these findings because reducing fatigue may be of crucial importance to increase the observance of antiviral therapy in chronic hepatitis C. In the future, it may be possible to better target serotonin reuptake inhibitors in individu-
als rather than using the current trial, thus giving the possibility of a more specific central effect.

L-carnitine

Carnitine is a hydrosoluble substance that plays a key role in the carriage of fatty acids from the cytosol into the mitochondria for oxidation and energy production [24]. It has been suggested that the administration of L-carnitine may enhance its intracellular level, while decreasing muscular weakness, low incidence of activity and also fatigue [25]. In an open label study, Cruciani et al. [26] have reported that 83\% of patients with fatigue related cancer had carnitine deficiency and that a one week of L-carni-
tine supplementation increased its plasma levels and relieved fatigue, depression and sleep disruption in a substantial propor-
tion of patients. In a recent study, it has been shown that high serum carnitine values allow a better response to interferon therapy, enhancing compliance and reducing some side-effects [27]. The role of car-

Substance P and neurokinin-1 receptor antagonists

The neuropeptide substance P and its receptor, the neuroki-
nin-1 receptor (NK\textsubscript{1}), have been implicated in the pathophysi-
ology of affective disorders, including depression and anxiety. Haddjeri et al. [29] have shown that, as occurs with other major types of antidepressants, substance P antagonists might alleviate anxiety and major depression, in part, by enhancing the levels of some 5-HT receptors in the forebrain. More recently, it was dem-

REFERENCES


Conclusion

From the data evaluated so far, there is evidence that 5-HT\textsubscript{3} receptor antagonists provide significant benefit in a substantial proportion of patients with chronic hepatitis C and fatigue. In clinical practice, our data justify a careful application with appropriate dosage to avoid adverse reaction (e.g. constipa-
tion). The duration of therapy still remains to be further explored. In addition, the recent reported adverse events from therapy of irritable bowel syndrome with alosetron provide a note for caution before a widespread use of such compounds to treat fatigue. Future development of more effective agents will depend both on a better understanding of the neural pathways and receptors involved in the control of fatigue, as well as on the investigation of new more selectively targeted compounds. At present, the treatment of fatigue in Hepatogastroenterology must be regarded at the threshold of transition from concept to well designed clinical studies.

ABBREVIATIONS:

FIS : fatigue impact scale
NK\textsubscript{1} : neurokinin 1


