Response to Letter to the Editor by Ernesto de Bernardis

Flavio Moroni Guido Mannaioni

Department of Neurofarba, University of Firenze, Florence, Italy

Dear Editor,

The target therapeutic plasma R-methadone concentration for the treatment of severe heroin users in the methadone maintenance program (MMT) described in Mannaioni et al. [1] was set at 80–250 ng/mL. The comment letter of de Bernardis suggests that by further increasing plasma R-methadone concentrations, a better therapeutic outcome could possibly be obtained. This suggestion is based on data published several years ago by Eap et al. [2].

When we selected the therapeutic window of 80–250 ng/mL of trough plasma R-methadone levels, we were certainly aware of the content of Eap et al. [2, 3] papers, which included the information that 93% of the MMT patients having plasma concentrations above 250 ng/mL of R-methadone do not use illicit opioids [2]. Our main goal was not limited to reduce illicit drug use, but we aimed to improve the percentage of patients retained in treatment for 1 year and to improve their quality of life. To reach this goal, we first selected 100–250 ng/mL as a reasonable therapeutic plasma concentration of the active methadone enantiomer. The selection was based

not only on our preliminary unpublished data but also on the careful evaluation of the content of the above-mentioned Eap et al. [2] publication (see the original protocol: Eudra C.T.2008-005028-10). In the first weeks of the trial, however, we realized that most patients in MMT having plasma R-methadone concentration between 80 and 100 ng/mL and having an acceptable quality of life refused to increase their daily methadone dose, and when the increase was repeatedly recommended, they preferred to abandon the trial. They feared the previously experienced methadone dose-dependent side effects, including constipation, excess sweating, drowsiness or other sleep disorders and decreased libido. Some of them were also aware that large doses of methadone may increase the Q-T interval and increase the risk of sudden death. On the basis of these preliminary observations, the trial steering committee decided to amend the protocol and to reduce the lower limit of the therapeutic window from 100 to 80 ng/mL of plasma R-methadone concentration. The upper limit remained at 250 ng/mL, but in our population, a very

limited number of patients reached such levels (Fig. 3a in Mannaioni et al. [1]). Furthermore, we confirmed that plasma concentrations above 200 ng/mL were reached in patients with an oral methadone dose intake of as low as 60 or as high as 200 mg/day (see the above-mentioned Fig. 3a). Eap et al. [3] reported that a plasma trough concentration of R-methadone of 250 ng/mL may be reached with doses as low as 55 mg/day or as high as 921 mg/day, thus making it particularly difficult to obtain high plasma R-methadone levels. A reasonable explanation of these data is based on the possibility that in a significant percentage of patients, large methadone doses may increase its own metabolism. It is probably worthwhile to outline that in our controlled trial, all the patients succeeding in maintaining R-methadone plasma concentration within the range of 80–250 ng/mL at 0 and 6 months continued to be benefited by treatment for the whole duration of the trial.

Our observations were in general agreement with the data published in the mentioned Eap et al. [2, 3] papers. These

papers report that 86 out of 99 MMT patients had plasma R-methadone concentration in the range of 50–175 ng/mL, while only 4 patients had plasma R-methadone concentration above 250 ng/mL (see the graph in Fig. 1 of Eap et al. [3]). Similar results were obtained by Meini et al. [4]. In their more recent report, at least 80% of the MMT patients had plasma R-methadone concentration in the range 50–150 ng/mL and only 4 patients had methadone concentration above 250 ng/mL (Fig. 2). Furthermore, the same paper states that the average plasma concentration of R-methadone in MMT patients not using illicit opioids was 93 ng/mL, while the average R-methadone concentration in plasma of the patients with opi-

oid positive urines was 77 ng/mL. We found that approximately 30 % of MMT patients with plasma R-methadone concentrations in the “target” range failed to stop their use of illicit opioids. However, a significant reduction of this use took place in the course of one year of treatment. It is therefore particularly important to obtain an “appropriate” methadone dose, which is able to improve retention in treatment.

In conclusion, “maintenance in methadone treatment” and “elimination of illicit heroin use” are different goals and may require a different pattern of R-methadone plasma concentrations. The therapeutic window of 80–250 ng/mL of R-methadone was selected to test the possibility of im-

proving the percentage of patients remaining in treatment possibly with an acceptable quality of life. The fear or the actual presence of side effects may prevent a significant percentage of patients to increase their daily methadone dose, thus leading to the abandonment of the therapeutic program. Finally, our data clearly suggests that the administration of an appropriate methadone dose is only one of the factors that may improve the life of patients with severe heroin use disorder.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

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