

## IS THE "DRUG HOLIDAY" HARMFUL?

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### ABSTRACT

The "drug holiday" has been recently supposed to be necessary in order to protect psychotic patients who have been taking neuroleptics for a long time against the occurrence of tardive dyskinesia. But from the fact that neuroleptics have some hormonal, metabolic and autonomic nervous effects besides mental ones, it is reasonable to assume that sudden intermittent withdrawal of neuroleptics ("drug holiday") is followed by rebound phenomena such as changes of blood pressure, increase of blood free fatty acids, increase of blood serotonin, and increase of growth-hormone release-inhibiting hormone etc. These rebound phenomena may be consistent with the ischemic heart diseases, the kinds of embolism, and the sudden deaths that are supposed to have a higher incidence among psychotic patients: and the obesity and diabetes that are supposed to be caused by neuroleptics. It remains, however, to be investigated how to decide and decrease the dosage of psychotropic drugs more safely.

### TARDIVE DYSKINESIA AND THE "DRUG HOLIDAY"

Tardive dyskinesia (persistent oral dyskinesia) is supposed to appear in chronic psychotic patients who have been taking neuroleptics(N.L.) for a long time. Some investigators say that the same kind of extrapyramidal symptoms which resemble tardive dyskinesia, sometimes occur during L-dopa treatment of parkinsonism.<sup>1,2,3</sup> They think this phenomenon is due to over dosage of L-dopa. On the other hand, from the fact that tardive dyskinesia often occurs when the drug treatment is suspended all at once, and many kinds of N.L. accelerate the turnover rate of noradrenaline(N.A.) and/or dopamine(D.A.),<sup>4</sup> long term N.L. treatment is supposed to cause dopaminergic receptor site hypersensitivity. In other words, because N.L. suppresses D.A. stimuli considerably over a long period, the dopaminergic receptors probably become sensitive to quite small amounts of D.A. stimuli, so that a sort of homeostasis may be kept by both of

these factors. If, therefore, D.A. stimuli is suddenly increased to a normal level by the closure of N.L. treatment, the receptors will react strongly to the larger amount of D.A. stimuli. There are some contradicting evidences, though.<sup>5</sup> From these and other points, many clinical psychiatrists insisted that N.L. treatment should be interrupted regularly, for instance one or two days a week, in order to keep the dopaminergic receptor at a normal level of sensitivity. This interruption is called now the "drug holiday".

The structure of this treatment is not different from hormonal maintenance therapy such as cortisol treatment. However, even granting that we may be able to protect the receptor site from hypersensitivity or prevent the N.L. induced tardive dyskinesia, it is still reasonable to assume that the "drug holiday" causes the rebound phenomena which affect the subjects' hormonal balance and autonomic nervous system(A.N.S.). These rebound phenomena may well be harmful to the subjects. The following sections will discuss first the findings of other investigators relevant to hormonal and other effects of N.L. treatment, and then their implications which are related to more clinical problems.

#### HORMONAL AND OTHER RELATED ITEMS

The release of prolactin from the hypophysis is controlled by the prolactin inhibiting hormone from hypothalamus which is activated by dopamine stimuli. The higher the dopaminergic stimuli and the prolactin inhibiting hormone level, the lower the prolactin level and its hormonal activity. Sacher and his coworkers demonstrated that the injection of N.L. into volunteers made the prolactin level increase rapidly,<sup>6</sup> and many investigators showed that N.L. induced galactorrhoea and loss of menstrual discharge is closely connected with the prolactin level<sup>7,8</sup> and moreover this level and clinical symptoms are easily decreased simultaneously by 2-bromo-ergocryptine(bromocriptine), a D.A. agonist.

Other hypophyseal hormones are also related to the releasing hormones or release inhibiting hormones of hypothalamus, most of which are supposed to be released by D.A. (e.g. gonadotropin-releasing hormone, thyrotrophin-releasing hormone, and growth-hormone release-inhibiting hormone). It has, incidentally, recently been shown that when the growth-hormone release-inhibiting hormone (G.H.R.I.H.) is given as a remedy for acromegaly, the platelet-count goes up significantly.<sup>9</sup> It is a common clinical experience that blood pressure usually goes down when N.L. treatment starts, and this has been explained as one of the symptoms of A.N.S. depression. This is quite consistent with the rise of N.A. turnover rate, one of the N.L. functions. Betablocking agents were introduced as a drug for angina pectoris, whereas it has been desmonstrated several times that the

betablocker withdrawal has an intimate relation with the occurrence of angina, arrhythmia and sudden death.<sup>10,11</sup> One of the possible explanations for this phenomenon is as a rebound effect of A.N.S.

Since the introduction of N.L. treatment, there have been many reports that more and more psychotic patients, especially institutionalized ones, showed obesity and diabetes mellitus.<sup>12,13,14,15,16,17</sup> There is no definite explanation for this relation between N.L. and obesity. But I would like to discuss some possibilities about this problem. First, the lipolysis of triglyceride of the adipose tissues is supposed to be activated by several kinds of hormones, such as A.D., N.A., serotonin, adrenocorticotrophic hormone (ACTH), G.H., and others,<sup>18,19,20,21,22,23,24,25</sup> hence this lipase is called the hormone sensitive lipase (H.S.L.). Cyclic A.M.P. is supposed to have a relation to this lipolysis, as the second messenger of hormonal function. As I mentioned before, N.L. makes the N.A.'s turnover rate go up and this means the blocking of the lipolysis of the triglyceride (T.G.) to free fatty acid (F.F.A.) and glycerol at adipose tissues while the F.F.A.'s re-esterification is intact. If the blocking of lipolysis is carried on continuously, more T.G. will be stored in the adipose tissues, and the subjects will get overweight. This explanation is consistent with the ideas of Curtis-Prior,<sup>26</sup> who assumed that obesity in general was due to the prostaglandin hyperactivity because prostaglandin was also supposed to inhibit the lipolysis of T.G. at adipose tissues.<sup>27</sup> F.F.A. on the other hand, has been shown to increase coagulability.<sup>28,29,30,31,32</sup>

The level of serotonin, one of the hormones that stimulate H.S.L., is shown to be higher in the blood of unmedicated chronic schizophrenics than in the blood of medicated schizophrenics, while the latter does not differ from that of control subjects.<sup>33</sup> This is consistent with the observation that the platelet monoamine oxidase activity is low,<sup>34,35</sup> and monoamine oxidase is deformed in those patients.<sup>36</sup> Clement-Cormier and his colleagues have recently found the adenylyl-cyclase, which is selectively stimulated by D.A. in a certain area in the brain, and whose enzyme activity was depressed by some kinds of N.L.<sup>37,38</sup>

#### IMPLICATIONS

From the findings cited above, I would like to suggest some possible hypotheses to show how harmful it is to stop drug treatment all at once.

During the "drug holiday", the prolactin level will fall down as the sequence of the N.L. withdrawal. This was shown at the weekly intervals by Beumont et al.<sup>8</sup> and at a couple of days interval by the author (unpublished data). This is a result of the increase of D.A. activity or hyperactivity of D.A. and I think it possible that G.H.R.I.H. will go up because of D.A. hyperactivity and cause

the impairment of platelet function. This, however, is still controversial. For instance, G.H. release is different in each other animal species. Plasma human G.H. was demonstrated to increase with the L-dopa load while an abnormally high level of G.H. in patients of acromegaly was suppressed by bromocriptine, a precursor of dopa. As regards the N.L.-induced diabetes, some reports showed that glucagon may play a vital role in glucose homeostasis and G.H.R.I.H. could suppress G.H. level, or in other words, be of therapeutic value in diabetes. It is not impossible, therefore, to speculate that N.L. depress the G.H.R.I.H. level and this is followed by an imbalance of glucose metabolism i.e. diabetes.<sup>39</sup>

Blood pressure will show some sort of changes from the reasons as I said before, and this may change the coagulability.

Hussar studied the leading causes of death in institutionalized chronic schizophrenic patients and control subjects, and found that the incidence of ischemic heart disease was higher in the former.<sup>40</sup> I assume that the "drug holiday" has the possibility of causing ischemic heart disease or sudden death because N.L. causes an imbalance of A.N.S. And I would like to add that some investigators assume the presence of dopaminergic receptor at the heart.<sup>41</sup> Snider drew attention to the release of peripheral D.A. during stress,<sup>42</sup> and we have to consider the fact that betablocker withdrawal is sometimes followed by arrhythmia, angina or sudden death. With regards to arrhythmia during acute myocardial infarction, high plasma F.F.A. level has been demonstrated as an arrhythmogenic factor, and lipid-lowering drugs such as a nicotinic acid analogue have been demonstrated to be an effective remedy for those arrhythmias. The latter point, however, is controversial.<sup>43,44,45,46</sup>

As aforementioned, N.L. suppresses the lipolysis of T.G. into F.F.A., and the increase of F.F.A. shortens the blood clotting time. So, it is possible that N.L. withdrawal forces the release of F.F.A. into the blood, and this causes a shortening of the blood clotting time. This may be correlated with the fact that some sorts of embolism and ischemic heart disease often occur in patients taking N.L.<sup>47,48,49,50</sup>

For the aforesaid reasons, the serotonin level may be depressed by N.L. and it will go up when N.L. is taken away. Admittedly, the physiological function of serotonin is not yet clear, but from the fact it is one of the hormones which stimulate H.S.L., it can be speculated that serotonin rise backs up the F.F.A. release more or less. In addition to this, some investigators demonstrated that serotonin as well as other catecholamines clumped platelets in various concentrations.<sup>51</sup>

Speaking of cyclic A.M.P., it will be possible in due time to explain the N.L. activity by using the concept of cyclic nucleotides and possible hormonal changes

that I have described, will be also deciphered by using this concept.

Thus there seem to be great risks of harmful complication from the "drug holiday", but most of psychotic patients, especially schizophrenics, need to receive drug treatment for many years because of their persistent symptoms. And besides the "drug holiday", drug treatment is occasionally interrupted, for instance when the patients refuse to take it, the nurses forget the administration or just after an operation of the gastrointestinal tract. Logically speaking dopaminergic hypersensitivity if it exists, will depend on the dosage and duration of N.L. treatment, but the critical dosage and duration is not known. And it is hardly known to what extent we can reduce that N.L. dosage without the hormonal, metabolic and nervous changes. These problems remain to be clarified, or in other words we should find a safer way of deciding, reducing and discontinuing the N.L. dosage. Through these steps, I am sure, we will be able to make the best of N.L. with fewer physical complications and less tardive dyskinesia alike.

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