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Biochemical and neuroendocrine approaches to a malignant syndrome of neuroleptics

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ABSTRACT

A 20 year old patient who has been hospitalized for depressive schizoidia is treated by nomifensine (75 mg/d) plus pimozide (4 mg/d).

Four days later, he shows a typical neuroleptic malignant syndrome (Syndrome malin de Delay et Deniker).

The biological explorations show that inflammatory blood tests are increased, hepatic tests are disturbed and the pituitary tests suggest a hypothalamic disturbance of the balance between NE and DA (reduced STH, FSH and LH) with a relative NE predominance, but also an increase of DA (increased HVA in CSF.

A pathogenic interaction between nomifensine, an antidepressant inhibiting the reuptake of NE and DA, and pimozide, a neuroleptic blocking dopaminergic postsynaptical receptors is to be considered (Acta psychiat. belg., *1980*, 80, *600-606*).

Key words : malignant syndrome, neuroleptics, antidepressants, nomifensine, pimozide, psychopharmacology.

The malignant syndrome

The malignant syndrome is « the most serious and the least known of all complications of neuroleptic chemotherapies » (Delay and Deniker, 1961)*. The symptomatology is characterized by hyperthermia, a «major» extrapyramidal syndrome (rigidity, akinesia...) and by «neurovegetative» troubles (coma, dyspnea, variations in the arterial pressure, trophic disturbances...).

If one doesn't treat with specialized equipment, the evolution is often fatal. The neuroleptics that are most incriminated are of the «incisive» type, especially haloperidol (Haldol®), thioproperazine (Majeptil®) and flufenazine (Anatensol®, Moditen®, Permitil®, Sevinol®). The physiopathology of the syndrome remains unknown and the treatment, which is solely symptomatic, calls for an intensive-care unit.

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Clinical observation

A 20 years old patient of Italian origin has been hospitalized in our department for *depressive schizoidia.* His familial and personal background is without any particularity, both on the medical and the psychopathological level. The present problems started six months ago and the patient has already received several psychotropic treatments without any improvement :

— haloperidol 3 mg/d,
— pimozide 8 mg/d + sulpiride 600 mg/d + procyclidine 4 c/d + lorazepam 10 mg/d,
+ triazolam 1 mg + clotiapine 40 mg when going to bed,
— idem + butriptyline 75 → 100 mg/d,
— idem + desipramine 75 → 175 mg/d.

A biological balance-sheet (blood, differential WBCC, platelets, inflammatory tests, ionogram) glycemia, urea, creatinin, hepatic tests, lipidic balance-sheet) has been established during the weaning period (48 hours). The results are normal.

The patient has been treated with *nomifensine* (75 mg/d) and *pimozide* (4 mg/d) (plus amobarbital : 100 mg when going to bed).

Nomifensine (Alival®, Meritral®, Lab. Hoechst) is an *antidepressant* derived from tetrahydroisoquinoline that inhibits the reuptake of noradrenaline (NE) and of dopamine (DA) in the presynaptical vesicles.

Pimozide (Orap®, Opiran®, Lab. Janssen) is a *neuroleptic* derived from diphenylbutylpiperidine, which blocks the postsynaptical dopaminergic mesolimbic and nigrostriated receptors.

* Delay J., Deniker J. *Méthodes chimiothérapiques en psychiatrie.* Paris, Masson, 1961.

After 3 days of treatment, symptoms that remind us of the « malignant syndrome » appear : troubles of consciousness (mutism, refusal to eat and to swallow) associated with a clear extrapyramidal syndrome (rigidity, hypersialorrhea).

On the 4th day, the patient presents a clinical picture that is typical of the «malignant syndrome». All psychotropic treatment is stopped. The lumbar puncture that is done on the following day is normal (pressure, chemical, cytologic and bacteriological analysis).

Clinically, the situation of the patient remains stationary and he is removed to the intensive-care unit. On the biological level, one notes gradual changes in the inflammatory tests and in the hepatic tests, and the EEG shows a global slowing down that becomes intensified. The cerebral « tomoscan » is normal.

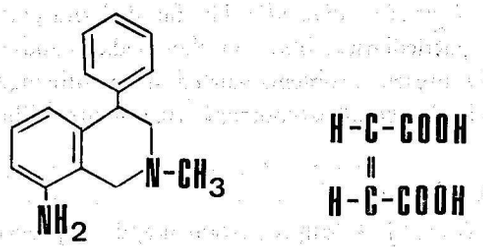

FIG. 1. — Structural formula of nomifensine.

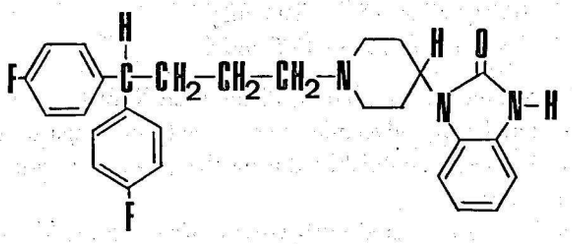

FIG. 2. — Structural formula of pimozide.

The biological balance-sheet that is realized on the 13th day hields the following results.

1. *Rise in the inflammatory tests :*

SR	= 32 mm	(N : 4 - 10)
fibrinogen	= 5,31 g/l	(N : 1,87 - 3,67)
leukocyte count	= 20.000/mm^3	(N : 4.300 - 10.600)
α 2 globulins	= 14 %	(N : 4 - 7)

2. *Alteration in the hepatic tests :*

conj. bilir.	= 13,8 mg/l	(N : 0 - 3,5)
unconj. bilir.	= 7,7 mg/l	(N : 1 - 7)
SGOT	= 41 mUI	(N : 0 - 30)
SGPT	= 75 mUI	(N : 0 - 30)
OCT	= 306 mUI	(N : 0 - 97)
LAP	= 92 mUI	(N : 0 - 60)
γ GT	= 186 mUI	(N : 0 - 50)
Alk. Pase	= 125 mUI	(N : 40 - 105)
5 - Nase	= 24,7 mUI	(N : 3 - 16)

3. *Pituitary balance-sheet (radio-immunology) :*

STH ↘	= 0,2 ng/ml	(N : 4,2 ± 2,15)
FSH ↘	= 0,4 mUI/ml	(N : 3,8 ± 2,2)
LH ↘	= 0,3 mUI/ml	(N : 2,4 ± 1,8)
TSH N ↗	= 2,1 ng/ml	(N : 0,77 ± 0,47)
PRL N ↗	= 264 UI/ml	(N : 172 ± 52)

4. *CSF :*

HVA (DA) ↗	= 102 ng/ml	(N : 25)
5-HIAA (5-HT) N	= 23 ng/ml	(N : 20)

Under symptomatic treatment as opposed to psychotropic treatment, the evolution of the patient becomes clinically favourable after 3 weeks. The inflammatory, hepatic and pituitary findings return to normal after 6 weeks.

Interpretation

The results of the endocrine balance (reduced STH, FSH and LH) suggest a rupture in the balance NE-DA in favour of NE. Yet, the rise in HVA, the main metabolite of DA, in the CSF points out a rise in DA. So this implies a *hypothalamic perturbation* in the sense of *an increase in the NE and DA proportions with a relative NE predominance.*

The unexpected arrival of the « malignant syndrome », when nomifensine and pimozide are combined, puts the question of a pathogenic interference between the two products. This is possible on the biochemical level : pimozide blocks the postsynaptical dopaminergic receptors, whereas nomifensine blocks the reuptake of DA.

The originality of this observation may lie in the fact that the « malignant syndrome », which is normally attributed to a neuroleptic, probably finds its etiopathogeny in the association of a neuroleptic with an *antidepressant.*

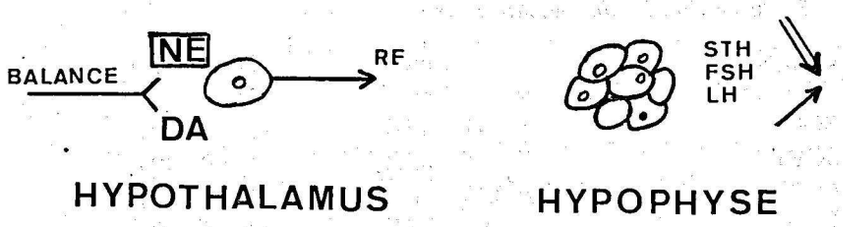

FIG. 3. — Hypothalamo-pituitary regulation of the secretion of STH, FSH and LH.

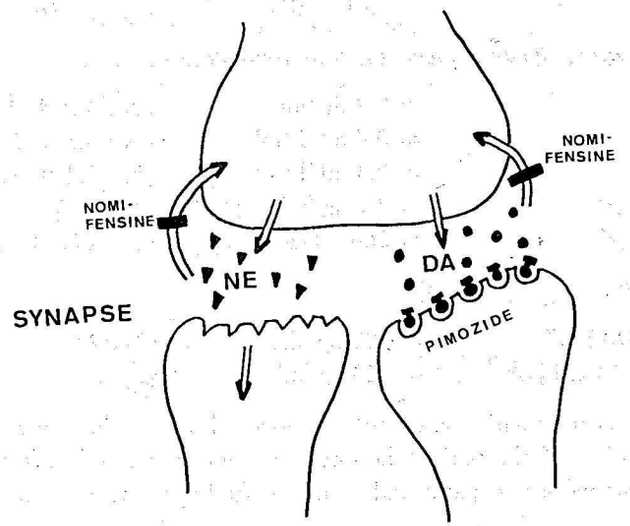

FIG. 4. — Comparative activities of pimozide and nomifensine on cathecholamines at the synapse.

Conclusions

This observation enables us to put forward the hypothesis of a perturbation of the hypothalamic regulation in the genesis of the « malignant syndrome ». There would be a concomitant rise in NE and DA with however a relative NE predominance. It appears that there is no modification of 5 HT. A pathogenic interaction between nomifensine and pimozide in the DA metabolism is possible.

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RESUME

Approche biochimique et neuro-endocrinienne d'un « syndrome malin » neuroleptique.

Un patient de 20 ans, hospitalisé pour schizoïdie dépressive, est traité par nomifensine (75 mg/j) et pimozide (4 mg/j). Après quatre jours, il développe un « syndrome malin » neuroleptique. Les explorations biologiques montrent une augmentation des tests inflammatoires, des altérations des tests hépatiques et le bilan hypophysaire suggère une perturbation hypothalamique de la balance entre la NE et la DA (STH, FSH, LH diminués) avec prédominance relative de la NE, mais aussi augmentation de la DA (HVA augmenté dans le LCR). Une interaction pathogénique entre la nomifensine, antidépresseur inhibant le recaptage de la NE et de la DA, et le pimozide, neuroleptique bloquant les récepteurs postsynaptiques dopaminergiques, est envisagée.

SAMENVATTING

Biochemische en neuro-endocriene benadering van een kwaadaardig neuroleptisch syndroom.

Een 20-jarige, voor schizoiede depressie, opgenomen zieke werd behandeld met nomifensine (75 mg p.d.) en pimozide (4 mg p.d.). De vierde dag vertoonde hij een « kwaadaardig neuroleptisch syndroom ». De biologische proeven wezen op een verhoogde ontstekingsreaktie, of afwijkende lever proover. De hypophysaire proeven doen denken aan een hypothalamische stoornis van de NE en DA verhouding (STH, FSH en LH vermindering) met betrekkelijke overheersing van de NE, maar met wel een verhoging van DA (met verhoogd HVA in het hersenvocht). De ziekte oorzaak kan wellicht gevonden worden in het samenwerken van nomifensine, een antidepressief middel, dat de heropname van de NE en DA remt met pimozide, dat de postsynaptische, dopaminergische receptoren afsluit.

RIASSUNTO

Approccio biochimico e neuro-endocrino ad una « sindrome maligna » neurolettica.

Un paziente di 20 a. ricoverato per schizoidismo depressivo é stato trattato con nomifensina (75 mg/pro die) e pimozide (4 mg/pro die). Dopo quattro giorni sviluppa una « sindrome maligna » neurolettica. Gli accertamenti biologici dimostrano un aumento dei test infiammatori, delle alterazioni dei tests epatici ed il bilancio ipofisiario suggerisce una disfunzione ipotalamica della bilancia tra NE e DA (STH, FSH, LH diminuita) con predominanza relativa della NE ma anche aumento della DA (HVA aumentata nel LCR). Viene ipotizzata un'interazione patogena tra la nomifensina, antidepressivo inibente la ricaptazione della NE e della DA, ed il pimozide, neurolettico bloccante i recettori postsinaptici dopaminergici.

RESUMEN

Aproximación al estudio bioquimico y neuroendocrino de un sindrome maligno neuroleptico.

Un paciente hospitalisado de 20 años, con esquizoidia depresiva, recibe como tratamiento 75 mg/dia de nomifensina y 4 mg/dia de pimozide. Quatro dias despues de empezar el tratamiento se desarolla un « sindrome maligno » neuroleptico. Los examenes de laboratorio demuestran un aumento de los tests inflamatorios y alteraciones de los tests hepaticos. El bilan funcional de la hipofisis suggiere una perturbación hipotalamica del balance entre la NE y la DA (STH, FSH, LH disminuidos) con predominancia relativa de la NE con aumento de la DA (HVA aumentado en el LCR). Se considera como posible una interacción entre la nomifensina y el pimozide : el primero inhibe la captación de la NE y de la DA ; el secundo, neuroleptico, bloquea los receptores postsinapticos dopaminergicos.

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Résultats des tests de stimulation par le facteur de libération de la thyrostimuline (TRF) et par le fragment 1-24 de l'hormone corticotrope chez des sujets traités au long cours par des neuroleptiques

Etude préliminaire

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ABSTRACT

Hormonal stimulation after injection of thyrotrophin releasing factor (TRF) and 1-24 ACTH in patients following chronic treatment with neuroleptics

Fifteen patients with neuroleptic treatment (haloperidol 4 to 6 mg a day or phenothiazines) and eleven control patients were given TRH 250 µg i.v. and 1-24 ACTH, i.m. different times, TSH, T3, T4, FT4, Prolactin (PRL), cortisol were measured.

Before TRH injection, at baseline, TSH is higher ($p < 0,01$) and T3 lower ($p < 0,05$) in the neuroleptics treated group than in the control group. These results suggest the occurrence of a biological hypothyroidism in the group with neuroleptics ; moreover PRL is significantly increased. After TRH injection the response is not significantly different between the two groups. Cortisol level is lower at baseline and after 1-24 ACTH injections in the group with neuroleptics (Acta psychiat. belg., *1980*, 80, *607-618*).

Key words : chronic treatment with neuroleptics, haloperidol, phenothiazines, tyrotrophin releasing factor, 1-24 ACTH.

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