The incidence of depression is on the increase among both the orientals\(^1\) as well as among the occidentals.\(^2\) The psychiatrists, the general practitioners and even the public at large are becoming progressively more and more interested in depression, its manifestations, its diagnosis, its evolution and its treatment. The topic of depression has been discussed in every psychiatric congress and symposium which took place anywhere in the world during the last five years. During this period of time in Europe, six psychiatric international gatherings were dedicated to depression only. Depressions in children were also discussed in two of them, while another conference was dedicated exclusively to the problems of depressions in children and adolescents.

This vivid interest in depression has been triggered mostly by the introduction of the antidepressant drugs. The latter made possible the treatment of masked depressions, in the case of which nobody would have dared to administered ECT because the low intensity of the accompanying pure psychopathologic manifestations. The initial diagnosis of masked depression is confirmed only when the syndrome subsides under antidepressant medication. On the other hand, masked depressions represent approximately 40% to 70% of the cases of depression encountered in private practice.

The concept of depression has been enlarged by the recognition and acceptance of the syndrome of masked depression. This explains the increase in the incidence of depression everywhere in the world. Increased is not the real incidence of depressions, which can never be estimated with any accuracy, but only the incidence of the cases of diagnosed depressions.

There is also an increased interest in the ambulatory treatment of depression, also due to the effectiveness of the thymoleptic drugs.\(^1,3\)

The critical observation of the clinical antidepressive effects of ECT brought the author to the recognition that ECT has an antidepressive action which while intensive, is limited mainly to the suppression and interruption of the depressive psychosis and of the depressive suicide. The patient loses the depressive delusions of sin, guilt, worthlessness, hopelessness and helplessness; he eats and sleeps well again. However, the depressive mood and the lowered inner drive persist in the majority of cases of depressions treated with ECT. Perhaps at some extent, ECT has an antisuicidal action because the inner drive is not lifted. Also do persist are most of the somatic equivalents of depression. The thymoleptics act complementary with the ECT: they lighten and brighten the mood, lift the inner drive and extinguish the somatic equivalents. For these reasons the thymoleptics are essential for the treatment of depressions, even in cases in which ECT is used and is effective.

Since not all depressions respond to the imipramine-like thymoleptics, thymoleptics of a different chemical structure

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are desirable, because they may prove effective in cases in which the former fail.\(^{19}\)

Such a “real new” thymoleptic is Istonil (dimethacrine “Siegfried”). It is a diphenylamine derivative of acridon, analogous to melitracen.\(^{4}\) It is use in Europe since 1967, i.e., already for six years.

Assessment of its pharmacodynamics and pharmacology has been published in four European papers.\(^{5,6,7,8}\)

There were not published any unfavourable reports about the clinical effectiveness of Istonil. Favourable assessments of the clinical effectiveness of Istonil have been published by various authors in at least seven European papers.\(^{3,9,14}\) Also the drug is mentioned as clearly and highly effective, especially in inhibited depressions in a European book about masked depressions\(^{4}\) as well as in another four European papers.\(^{15-18}\)

**Methodology**

Because only endogenous and endoreactive depressions respond in a large proportion of cases and in a clear-cut fashion to the antidepressant action of the thymoleptics, thirty two cases of depressions of endogenous and endoreactive nosology were studied in the present trial of the effectiveness of Istonil.

With regard to age, the youngest patient was 12 years old and the eldest 66 years. Some of them were male and other female.

For the evaluation of the intensity of depression and its phenomenological spectrum, as well as for the assessment of the response to medication was used an own scale with fifty points of symptomatology, The index of depression before and after treatment was obtained by multiplying by two of the number of symptomatological points found in each case. With this personal scale, the highest index of depression—found outside of the present series of patients was 70%; while in the here presented 32 patients the highest was 54% and the lowest 10%. Therefore, in the present series the depressions have been between mild and moderately severe in intensity.

The author’s own scale of intensity and extent of depression and of the therapeutic results is designed. A personal scale of depressive index was badly needed because the Hamilton scale is not only too old, but also too simple and too vague and does not offer a compact basis for an appropriate and satisfactory clinical assessment of depressions and of the therapeutic results of antidepressant treatment.

Istonil was given orally in a dosage of 50 mg to 200 mg per day and in intramuscular injections in the dosage of 25 mg once per day. The duration of medication has been between two weeks and twelve months. The drug was taken per os in four daily fractionated doses. All patients received also daily and orally either a minor tranquilizer or a neuroleptic, and several patients also a hypnotic at bedtime.

All patients were seen daily during the first three weeks of treatment and later only once per week. This attitude permitted a close observation of the unfolding of the antidepressant action of Istonil.

**Results and Evaluation**

In the present series all the thirty two patients were orientals, Thai, Chinese and Indian.
The degree of improvement, i.e., the therapeutic index was estimated by comparing the index of depression before and after treatment as well as the percentage of persisting symptoms after two or three weeks of thymoleptic medication. (See Table 1 and Table 2.)

| Table 1. |
| Criteria for Estimating the Degree of Improvement, i.e., the Therapeutic Index |

| 1 - Excellent | 0 - 25% persistence of symptoms |
| 2 - Markedly Good | 26 - 40% persistence of symptoms |
| 3 - Fair | 41 - 60% persistence of symptoms |
| 4 - No Change | 61 - 100% persistence of symptoms |

Among the 32 cases of depressions on trial with Istonil, 15 cases were of endogenous depression and among them were 7 cases of endogenous masked depression. There were also another 17 cases of endoreactive depression, among which 7 cases were of endoreactive masked depression. All cases of masked depression responded well to the thymoleptic medication, a fact which confirmed the accuracy of the diagnosis.

The total of 14 cases of masked depressions in the present trial constitutes a percentage of 43.7% of the total of 32 cases of depression studied. This percentage is not too high, since in general practice it has been found that masked depression can represent up to 73% of all cases of depression detected. (1)

There were 5 cases of frank depressive psychosis and 7 cases of borderline depressive psychosis. Not all cases of endogenous or endoreactive depression reach the psychotic depth; however, they still remain endogenous or endoreactive. (1, 19)

The response to the antidepressive medication with Istonil has been satisfactory in 28 cases of endogenous and endoreactive depression, i.e., in 87.5% of the cases.

This result is very similar to that obtained with ECT in depressions of endogenous and endoreactive nosology. (22)

Among these 28 cases the response was excellent in 12 cases, i.e., in 37.5% and markedly good in 16 cases, i.e., in 50% of the cases.

The response was unsatisfactory i.e., "Fair" and "No change") in 4 cases, i.e., in 12.5% of the cases.

The dosage was 100-125 mg per day in 28 of the 32 cases studied. The lowest dosage was 50 mg per day in a boy 12 years old. A dosage of 200 to 225 mg per day was needed only in 3 more severe cases. This does not mean that the orientals need lower dosages of thymoleptics than the occidentals, but means only that the majority of the cases studied here were depressions of only moderate intensity. A maximum of 225 mg of Istonil per day for ambulatory depressive patients has been reported also by others in Europe. (14)

Among the thirty two cases studied were five children and adolescents: two 12 years old, two 14 years old and one 16 years old. Four of the youngsters received 100 mg of Istonil per day, per os. Two of them, one 14 years old and the other 16 years old received also Istonil 25 mg
per day in intramuscular injection. All
five youngsters had a perfect tolerance to
the drug and the depression was effectively
and rapidly controlled by Istonil in all
these five cases.

The five depressive youngsters repre-
sent 15% of the present series of 32 depres-
sed patients. It has already been reported
that the diagnosis of depression in children
is only too often missed (20) and juvenile
depressions take usually the form of disor-
ders in scholastic performance and in
behaviour. (20, 21)

There were three patients in age over
60 years: one was 64 years old and an-
other two were 66 years of age. They
received a dosage of 100 mg Istonil per
day orally and one of them also received
25 mg Istonil per day in intramuscular
injections. The drug was well tolerated
—as already previously reported by others
(10) — by all three elderly depressed pa-
tients. This is remarkable since Istonil is
an antidepressant which firstly lifts the
inner drive and since thymoleptics with
similar properties can cause delirious
states in the elderly. (18)

Both in the case of the juvenile depres-
sions and of the cases of depressions in
the older, the number of investigated
cases is too small to have any statistically
significant meaning. Therefore, in the
young and the old the dosage of Istonil
should begin with 12.5 mg, i.e., half a
tablet bid, then tid and finally qid, i.e.,
it should be initially only 25 mg per day
and thereafter the increase in dosage should
be gradual and slow. Such increments
should not take place at intervals shorter
than a minimum of three days. Before
age 18 years and as well after age 55
years, the dosage of Istonil should be kept
as much as possible to a maximum of 100
mg per day. The risk of higher dosage in
the young is the occurrence of marked,
dramatic restlessness, anxiety and agitation
and in the old the causation of a transient,
"exogenous" organic brain syndrome of
confusion or delirium. Should these occur,
the administration of the thymoleptic
should be immediately stopped. However,
in about seven days after the situation
has cleared up, the thymoleptic can be
given again, but in correspondingly lower
dosage. In case that the immediate result
of the withdrawal of the thymoleptic is
the appearance of vomiting, a neuroleptic
such as Stelazine (trifluoperazine) should
be given in a dosage of 0.5 mg to 1 mg
q.i.d. orally or in intramuscular injections.
Similar precautions should also be taken
with any other thymoleptic, since all of
them can cause similar complications.

In 22 cases, i.e., in 73.33% of the
cases, the latency period of Istonil, i.e.,
the period between the beginning of the
medication and the appearance of the first
antidepressive effects, was between 3 and
4 days. This is much shorter than in the
case of Tofranil (imipramine), Neodil
(dibenzapine) and Agedal (noxiptiline),
for which the average period of latency is
about 6 to 7 days, and it is the same as
that of Aventyl (nortriptyline).

In 24 patients, i.e., in 80% of the
cases, the full antidepressive effect of
Istonil set in between the 7 th and the
11 th day of medication, which again is
shorter than in the case of Tofranil, Neodil
and Agedal (approximately 16 days) and
the same as in the case of Aventil.

Istonil has been administered up to
one year in several patients without any
untoward phenomena.

All patients received either a minor
or major tranquilizer and in one case
both of them. The author has already
previously reported that the thymoleptic medication always demands also a concomitant medication with either minor tranquilizers or with neuroleptics, or with both of them. A hypnotic at bedtime is also often needed.\(^{(19)}\) Other authors have also indicated a similar procedure in the handling of thymoleptic medications.\(^{(4,17)}\)

Although all thymoleptics have an anti-anxiety component of activity, this does never suffice to counteract the depressive anxiety which is always intensified by the inner drive lifting component of activity of all tricyclic antidepressants.\(^{(19)}\) This is often the case even with Laroxyl (amitriptyline) and Surmontil (trimipramine), which have a nearly neuroleptic-like anti-anxiety action. In the case of Istonil, the need for the use of anti-anxiety adjuvant medication has been already mentioned and justified by a series of other authors also.\(^{(4,14,15,17)}\)

The switch over from depression to hypomania, even mania, with Istonil has already been reported.\(^{(15)}\) Actually all thymoleptics can induce such a thymic switch.\(^{(19)}\) In our present series one patient became restless, though not hyperthymic. The restlessness was actually the manifestation of an anxious agitation induced by the thymoleptic and responded well to an increase in the dosage of the already administered minor tranquilizer; this happened after four months of combined medication consisting in Istonil 100 mg per day and diazepam 8 mg per day. In another three patients a genuine hypomanic state occurred, demanding an increase in the dosage of neuroleptics already administered together with Istonil for periods of from three weeks up to four months prior to the thymic switch. Apparently the development of the hypomanic state was not related to the dosage of Istonil; two of the patients who became hypomanic took only 100 mg of Istonil per day and only one patient received 225 mg per day.

Istonil has also been administered in the thirty-third patient not included in the statistics of this series of 32 patients. This patient has a chronic paranoid schizophrenia and chronic schizophrenic depression. However, under medication the patient remains 100% free of symptoms and functions well as a teacher. The previous medication consisted of Melleril 400 mg per day and Tofranil 100 mg per day. With the replacement of Tofranil by Istonil 100 mg per day there was no relapse of depression. However, after 11 days on Istonil 100 mg per day the patient reported somatic delusions which subsided promptly when Istonil was withdrawn and Tofranil reinstated. Therefore Istonil activated the schizophrenia despite the co-administration of 400 mg Melleril per day, a dosage which was sufficient to prevent such activation of the psychopathology when Tofranil was the thymoleptic used. This fact seems to confirm the conclusion that Istonil has a more potent action than Tofranil in lifting the inner drive.

All thymoleptics have these two properties: to be able to induce a switch from depression to hypomania, even mania and also to activate a latent schizophrenia. The fact that Istonil showed these two characteristic activities is another proof that dimethacrine is a potent and effective antidepressant.

Istonil, though it has an intensive antidepressant activity has only few and insignificant anticholinergic side effects.\(^{(18)}\) In the present series of 32 patients only 4 of them, i.e., only 12.5% of the cases
studied presented such side effects, however, of low intensity; namely one case each complained of dry mouth and throat, of tachycardia and palpitations, of dizziness and of blurred vision.

Conclusions

This is a non-controlled study of the effectiveness of Istonil (dimethacrine “Siegfried”) in private practice, in ambulatory patients.

Though controlled studies are of value, reports based on the clinical experience of clinicians with extensive experience in their fields are often more reliable than many conventionally undertaken studies. (23) Because it is a very difficult task to collect a reasonable homogenous sample of even only 20 or 30 depressed patients (24) the present study has spread over a period of slightly more than one year.

The patients served as their own controls.

Istonil has been found to be an effective antidepressant whose main actions are the brightening of the mood and especially the lifting of the inner drive. It can be used as all other tricyclic thymoleptics in both inhibited and agitated depressions. However, like all other antidepressants, the patient should always receive concomitantly a minor or major tranquilizer, sometimes even both of them, and often also a hypnotic at bedtime.

However, Istonil seems not suitable in cases of agitated depression with marked free-floating anxiety, in which amitriptyline and trimipramine have an obvious advantage because of their more intensive anti-anxiety activity.

Istonil is especially indicated in the inhibited, apathetic depressions with marked psychomotor retardation.

In its psychotropic activity, Istonil has practically the same pharmacodynamic properties as Aventyl, which has also a rather low anti-anxiety action. (19)

A dosage of 50 to 100 mg per day is safe for youngsters of 12 years of age and older. For adult ambulatory depressives, a dosage of 100 to 225 mg per day is free of untoward effects which might force the withdrawal of the drug.

Istonil has been given in 10 ambulatory patients besides per os also concomitantly by intramuscular injections of 25 mg Istonil once per day and without any complaints or complications. Among these 10 patients the lowest pre-medication orthostatic blood pressure was 98–60 mm Hg. Others have also found that Istonil has practically no hypotensive action when taken per os in moderate dosage. (10)

However, when more than one intramuscular injection of Istonil per day is given, the patient should be hospitalized and kept continuously in bed in order to avoid dramatic orthostatic hypotension. But in such cases of apathetic, inhibited depression, near to the state of depressive stupor, the concomitant administration of ECT will contribute to a considerable reduction of the suffering of the patient; of this is the case Istonil should not be given in injection.

Anticholinergic side effects are extremely rare and very mild with Istonil, and do not lead to the withdrawal of this thymoleptic.

References


การใช้ยาแก้เเจ็บได้เม็ดครั้งในคลินิกส่วนตัว

เจน พองงค์, M.B.B.S., M.D.*

ผู้รายงานให้ใช้ยาได้เม็ดครั้ง (ซึ่งมีชื่อการค้าว่า อิซิไลซ์) ในผู้ป่วยเสรี
33 ราย ซึ่งมีอายุพักในคลินิกส่วนที่ 5 รายเป็นโรคข้อหัวเข่า 3 รายเป็นโรค
เข่าไม่เห็นไข้ในโรคข้อเข่า ทุกคนเป็นชาว
ครบถ้วน และให้ร้อยละดั่งประสาทชนิด
หลัก หรือชนิดของรูป ได้ให้ยาตาม
100 - 300 มก. ต่อวัน บางรายได้รับยา
ยาเดย์ลัม 15 มก. การรักษาไม่เวลา
2-3 ปี

ผลที่ได้ปรากฏว่า ยาเม็ดครั้ง ออก
ฤทธิ์แก้เเจ็บอย่างมีประสิทธิภาพ ไทย

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