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Region specific distribution of levomepromazine in the human brain

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Summary. *Objective:* The aim of this study was to examine concentrations of levomepromazine and its metabolite desmethyl-levomepromazine in different regions of human brain and in relationship to drug-free time.

Methods: Drug concentrations were measured in up to 43 regions of 5 postmortem human brains of patients previously treated with levomepromazine. To enable statistical comparison across brain regions several smaller brain areas were put together to form larger brain areas (cortex cerebri, limbic system, cerebellum, basal ganglia, thalamus). Mean values of drug concentrations in these larger brain areas were used in a repeated measurement ANOVA to analyze for region specific distribution. The elimination half-life in brain tissue was estimated with a NONMEM population kinetic analysis using the mean value of all brain regions of an individual case.

Results: Levomepromazine and desmethyl-levomepromazine appear to accumulate in human brain tissue relative to blood. Mean concentrations differed largely between individual brains, in part due to differences in dose of drug, duration of treatment and drug-free time before death. There was an apparent region-specific difference in levomepromazine concentrations with highest values in the basal ganglia (mean 316 ng/g) and lowest values in the cortex cerebri (mean 209 ng/g). The elimination half-life from brain tissue is longer than from blood and was calculated to be about one week. Similar results were obtained with desmethyl-levomepromazine.

Conclusions: Levomepromazine shows a region-specific distribution in the human brain with highest values in the basal ganglia. This might be the consequence of low expression of the metabolic enzyme Cyp2D6 in the basal ganglia. If this finding is true also for other neuroleptic drugs it might increase our understanding of preferential toxicity of neuroleptic drugs against basal ganglia structures and higher volumes of basal ganglia of neuroleptic-treated patients. Furthermore, patients exposed to levomepromazine cannot be considered to be free of residual effects of the drug for a number of weeks after withdrawal.

Keywords: Human, postmortem brain, pharmacokinetics, levomepromazine, neuroleptic drug, region-specific distribution.

Introduction

Neuroleptic drugs exert their clinical effects in part via cell surface receptors. Binding to cell surface receptors has been extensively studied in animal experiments, in *postmortem* human brain tissue and *in vivo* using PET and SPECT techniques. However, despite their extensive clinical use little is known about the accumulation, elimination half-life and regional distribution in brain tissue. We have previously shown that haloperidol accumulates in human brain tissue reaching concentrations 20–30 fold higher than blood concentrations optimal in the treatment of schizophrenia (Kornhuber et al., 1999). Furthermore, the elimination half-life of haloperidol from human brain was about 1 week (Kornhuber et al., 1999), which is also different from values obtained in the blood. The aim of the present study was to learn more about the regional distribution of neuroleptic drugs in human brain tissue. Brains of patients treated with levomepromazine were used for this study.

Subjects and methods

Brain tissue

Brain tissue was taken at autopsy from 5 subjects who had been treated orally with levomepromazine. These brains were collected between 1987 and 1994 and came from the Austrian-German Brain Bank Wuerzburg. A detailed examination of case notes was made to establish the duration and dosage of levomepromazine as well as the drug-free time before death. The drug-free time was calculated as the difference between time of last intake of the drug and time of death. The postmortem time was calculated as the difference between time of death and freezing of brain tissue. Histories of these patients with prescribed drug dosages, duration of treatment, drug-free time before death and concomitant medication are compiled in Table 1. Tissue samples were taken from 17 to 43 different brain regions from either side of the brain. It was not possible to investigate tissue samples of all these regions from every brain. Brain samples were also collected from patients who had never received levomepromazine. Postmortem handling of the autopsy material was similar in all cases and was performed according to a standardized procedure (Gsell et al., 1993). The samples were placed in a freezer at −80°C until analysis. Duration of storage at low temperature was between 4 and 11 years.

Materials

Levomepromazine was kindly donated by Bayer Vital, Leverkusen, Germany. N-desmethyl-levomepromazine and levomepromazine sulfoxide were obtained from the Department of Forensic Medicine, University of Mainz, Germany. Acetonitrile (HPLC grade) and sodium perchlorate monohydrate (p.a.) were obtained from Merck (Darmstadt, Germany). Water was deionized and filtered through a Milli-Q water processing system (Millipore, Eschborn, Germany). All other chemicals were purchased from usual commercial sources and were of the purest grade available.

Table 1. Case data, levomepromazine treatment and concomitant medication in individual cases

Patient number	Age (years)	Sex	Postmortem interval (hrs)	Daily oral dose (mg)	Duration of treatment (days)	Drug-free time (days)	Concomitant medication
1	71.8	f	9.8	25.0	1	4.2	
2	93.8	f	10.9	12.5	1607	0.2	
3	84.1	f	12.5	37.5	28	1.2	digitoxin, aminophylline, ambroxol, amiloride, lactulose, flunitrazepam
4	94.4	m	40.7	6.25	11	1.0	aminophylline, doxycycline, levothyroxine, allopurinol, haloperidol, ambroxol
5	87.2	f	3.6	12.5	16	16.5	dihydroergotamine

The drug-free time was calculated as the difference between time of last intake of the drug and time of death. The postmortem time was calculated as the difference between time of death and freezing of brain tissue

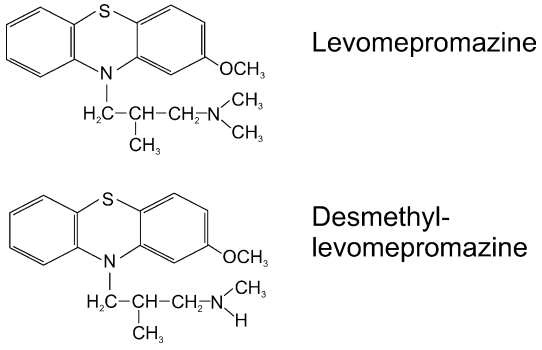

Fig. 1. Chemical structures of levomepromazine and desmethyl-levomepromazine

Determination of levomepromazine and metabolites in brain tissue

Levomepromazine and N-desmethyl-levomepromazine (Fig. 1) were analyzed by a high performance liquid chromatographic (HPLC) method with on-line column switching and ultraviolet detection. The method had been developed for determination of clomipramine and metabolites (Weigmann et al., 1998). The HPLC-procedure could be applied without further modifications to analyze levomepromazine and its two major metabolites in brain tissue extracts.

Brain samples were cleaned of visible blood, weighed, and frozen tissue (100 to 200 mg wet weight) was homogenized in four volumes of methanol using an ultra-turrax for 30 sec. Homogenates were centrifuged at 13,000 g and the clear supernatants analyzed for levomepromazine, desmethyl-levomepromazine and levomepromazine sulfoxide. Methanolic brain extracts were injected into the HPLC system without further purification. Drugs were retained on a cyanopropyl (CPS) coated clean-up column (10×2.1 mm I.D.; ict, Bad Homburg, Germany). The clean-up column was rinsed for 5 min with 20% (V:V) acetonitrile in deionized water at a flow rate of 1.5 ml/min. After switching of a six-port valve at 5 min, the analytes were eluted from the clean-up column and separated on LiChrospher CN (5 µm particle size) in an analytical column (250×4.6 mm I.D., MZ Analysentechnik, Mainz, Germany) at a flow rate of 1.5 ml/min using 38% (V:V) acetonitrile and 62% aqueous sodium perchlorate (0.02 M, pH 2.5). A variable wavelength ultra violet (UV) detector, type SPD-10A (Shimadzu, Kyoto, Japan) was used to monitor absorption at two different wavelengths (214 and 254 nm) simultaneously. The retention times were 15.5 min for levomepromazine, 14 min for N-desmethyl-levomepromazine and 6.5 min for levomepromazine sulfoxide (Fig. 2). Quantitative evaluation of chromatograms was performed at 254 nm

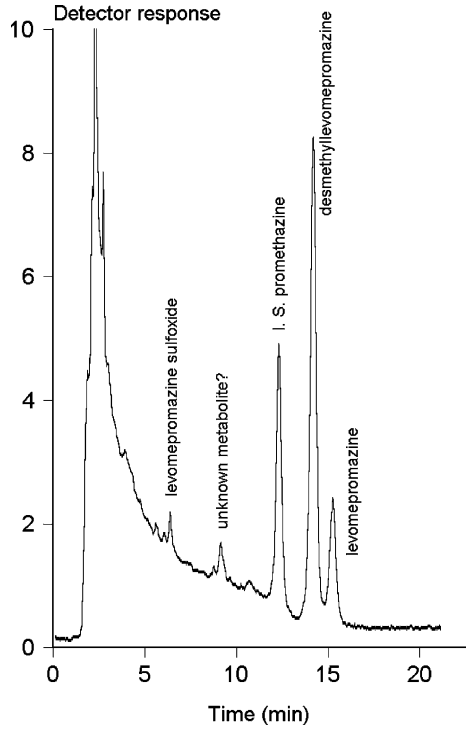

Fig. 2. Representative chromatogram (case #5, nucleus accumbens). The internal standard promethazine was added to the methanol used for extraction at a concentration of 1 µg/ml. Methanolic brain extract was measured; 66 ng/ml levomepromazine correspond to 296 ng/g brain concentration; 288 ng/ml desmethyl-levomepromazine correspond to a brain concentration of 1441 ng/g. Levomepromazine sulfoxide had a very low recovery rate of 20% and could not be quantified because of the small amount of pure substance available

using a commercial integration software PCIP (Kontron, Milan, Italy). Promethazine served as internal standard. The limit of quantification was about 15 ng/ml for levomepromazine and desmethyl-levomepromazine. The coefficients of variation ranged between 6 and 9%. Recovery rates from brain ranged between 46 and 55% for levomepromazine and between 39 and 41% for desmethyl-levomepromazine. Levomepromazine sulfoxide had a very low recovery rate of 20% and could not be quantified because of the small amount of pure substance available. Levomepromazine and desmethyl-levomepromazine were not detectable in brain tissue samples of patients never treated with levomepromazine. Drug content was expressed relative to the wet weight of brain tissue (ng/g). A representative chromatogram is shown in Fig. 2.

Statistics

Data were analyzed in an exploratory manner. A repeated measurement ANOVA with a post-hoc Scheffé-test was used to analyze for region specific distribution of levomepromazine, desmethyl-levomepromazine and the ratio between them. Not all brain regions were available for every patient. To allow ANOVA statistics with all cells filled up, several smaller brain regions were grouped to form larger brain areas:

"cortex cerebri" (cortex frontalis pol., cortex frontoorbitalis, cortex frontalis convexity, gyrus praecentralis, cortex temporalis, cortex temporalis superior, cortex temporalis medialis, cortex temporalis inferior, lobulus parietalis superior, gyrus postcentralis, gyrus angularis, gyrus supramarginalis, cortex occipitalis, cortex occipitalis pol., gyrus calcarinus superior, gyrus calcarinus inferior)

"limbic system" (gyrus cinguli, hypothalamus, trigenum habenulare, corpus mamillare, substantia innominata, corpus amygdaloideum, regio entorhinalis, hippocampus)

"cerebellum" (nucleus dentatus, cerebellum)

"basal ganglia" (nucleus caudatus caput, nucleus caudatus corpus, nucleus caudatus cauda, putamen, putamen pars anterior, putamen pars dorsolateralis anterior, putamen pars medialis, putamen pars dorsolateralis medialis, putamen pars posterior, nucleus accumbens, globus pallidus anterior, globus pallidus pars lateralis, globus pallidus pars medialis, globus pallidus pars ventralis, striatum)

"thalamus" (thalamus nucleus anterior, thalamus nucleus ventralis anterior, thalamus nucleus ventralis lateralis, thalamus nucleus medialis, thalamus nucleus medialis dorsalis, thalamus nucleus centromedianus)

"other brain areas" (corpus callosum, locus coeruleus, plexus choroideus, substantia nigra, substantia nigra pars compacta, nucleus ruber, nucleus subthalamicus, corpus geniculatum laterale, pulvinar, mark, broca region)

Mean values of drug concentrations were calculated for these larger brain areas and were used in the ANOVA to determine region-specific differences. "Other brain areas" were excluded from this analysis because of their heterogeneous composition.

For comparison of interindividual differences, mean values of drug concentrations were calculated using data from all brain regions. Since there was only a single measurement per individual in various brain regions and not sufficient data to describe the pharmacokinetic profile in each individual patient, a population pharmacokinetic analysis was performed using the computer software program NONMEM (Beal and Sheiner, 1992). The aim of this analysis was to estimate the average half-life of levomepromazine and desmethyl-levomepromazine in brain tissue in the population of patients investigated. Several assumptions had to be made: Steady-state conditions in brain tissue were assumed when the duration of treatment was 5 or more days, otherwise multiple dosing was modeled (case #1, Table 1). The intraindividual variability was fixed to the estimated coefficient of variation of the analytical method, i.e. 10%. Individual Bayes-posthoc estimates were calculated for the volumes of distribution. For the mean subject in the population a dose of 18.75 mg levomepromazine per day and steady state conditions were used. Subroutines ADVAN1, TRANS1 and SS1 of the package NONMEM V, level 1, were used. The pharmacokinetic model was:

$$C = \frac{D \cdot 1000}{V} \cdot e^{(-k \cdot t)}$$

where C = concentration (ng/g), D = dose of drug (mg), V = volume of distribution (l), k = elimination constant (1/h) and t = drug-free time after last dose (days).

The model describes the concentration-time curves in a one-compartment model after bolus-injection. The estimation of an absorption constant was not attempted due to the low number of data points. Because of the small sample, estimated values for V and k had large standard errors. Therefore, variability of these parameters was estimated using a bootstrap method. Repeated random samples with replacement were drawn ($n = 5$) from the original data set and analyzed using the model described. Mean values are given $\pm$SD.

Results

Levomepromazine concentrations in patients previously treated with the drug, ranged from 36 ng/g (plexus choroideus, case #4) to 858 ng/g (putamen, pars posterior, case #3). Desmethyl-levomepromazine concentrations ranged from 17 ng/g (corpus mamillare, case #1) to 1472 ng/g (nucleus medialis thalami, case #5). In each individual brain, levomepromazine and desmethyl-levomepromazine concentrations were highly correlated to each other (correlation coefficients between 0.68 and 0.98, $P < 0.01$).

With the repeated measurement ANOVA levomepromazine concentration in the larger

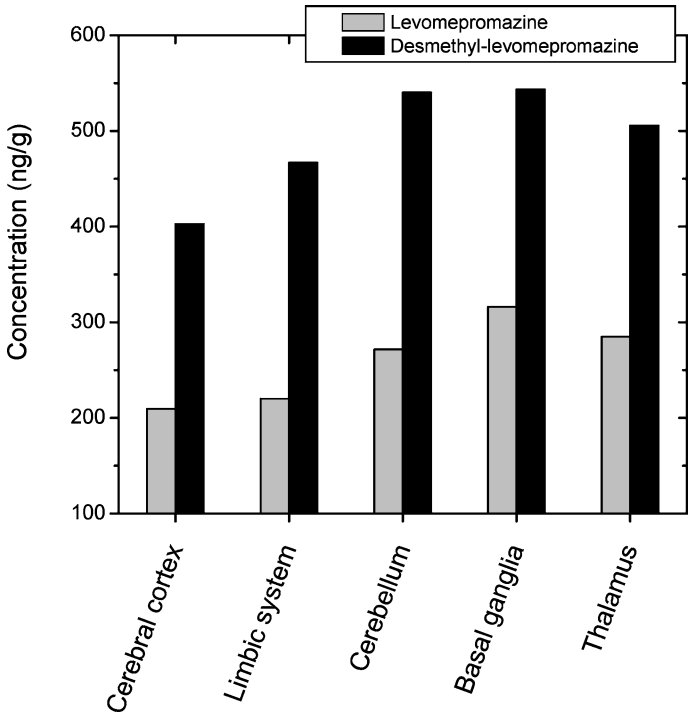

Fig. 3. Regional distribution of levomepromazine and desmethyl-levomepromazine in human brain tissue. Several smaller brain regions were combined to calculate a mean value for a larger brain area. The dataset contained 5 cases with 5 larger brain areas each. A repeated measurement ANOVA was calculated. The columns represent mean values from all 5 cases for a given brain region

brain areas was region-specific ($F = 4.43$, $P = 0.013$) with highest concentrations in the basal ganglia (316 ± 219 ng/g) and lowest concentrations in the cortex (209 ± 136 ng/g) (Fig. 3). The post-hoc Scheffé test indicates a significant difference in the cortex vs. basal ganglia ($P < 0.05$). A parallel situation was observed with desmethyl-levomepromazine concentrations; however this did not reach statistical significance (ANOVA, $F = 2.02$, $P = 0.14$). The ratio between levomepromazine and desmethyl-levomepromazine did not exhibit a region-specific distribution.

The interindividual differences between patients were considerable. Figure 4 shows mean levomepromazine and desmethyl-levomepromazine concentrations in brain tissue in relationship to duration of treatment, dose of drug and drug-free time before death. There was no apparent relationship between duration of treatment and mean levomepromazine concentration. Even after treatment with a single dose, considerable brain concentrations were measured.

In the population kinetic analysis using NONMEM a brain-elimination half-life of 7.9 days for levomepromazine and 27.8 days for desmethyl-levomepromazine were calculated for the mean subject ($k = 0.00365$ 1/h, $V = 214.9$ l for levomepromazine and $k = 0.00103$ 1/h, $V = 517.6$ l for desmethyl-levomepromazine). Similar values were obtained using the bootstrap method, which also provided estimates of the precision of the calculated elimination constant ($t_{1/2} = 7.5$, $+2SD = 7.0$, $-2SD = 8.1$ days for levomepromazine; $t_{1/2} = 28.6$, $+2SD = 26.1$, $-2SD = 30.9$ days for desmethyl-levomepromazine).

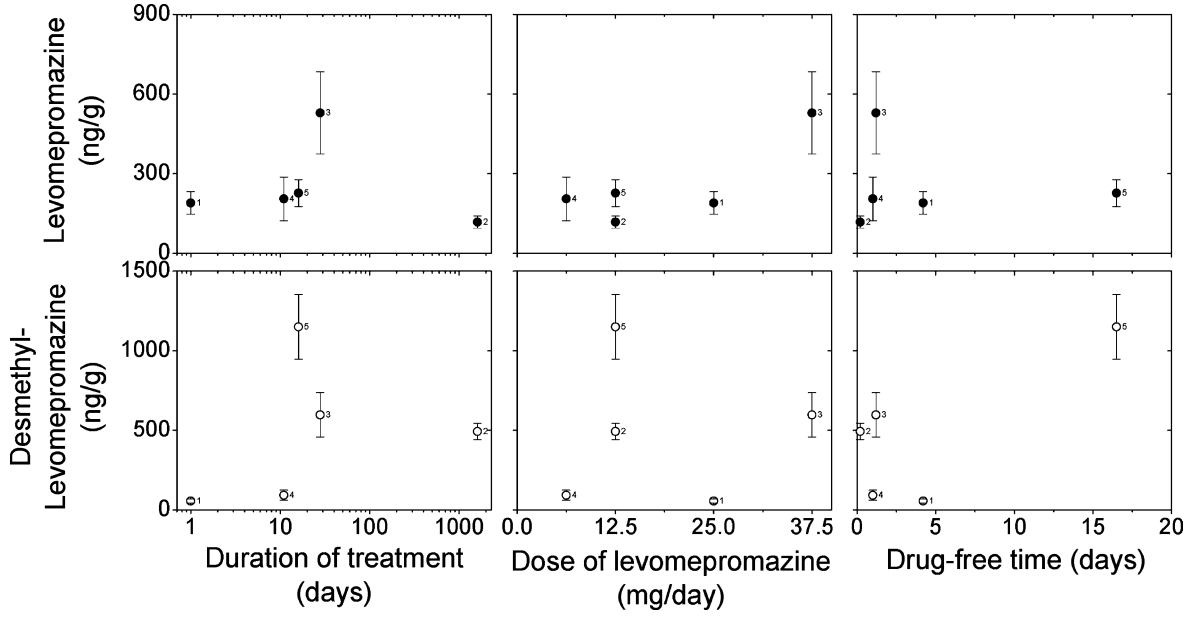

Fig. 4. Means of concentrations measured in different brain areas were calculated. Mean ± SD values of levomepromazine and desmethyl-levomepromazine concentrations are given for individual patient. There is no apparent impact of duration of treatment, of daily dose or of drug-free time on mean levomepromazine or desmethyl-levomepromazine concentration in brain tissue. However, the combined analysis of these parameters using the population kinetic approach and the NONMEN software results in elimination half-lifes of about one week and one month for levomepromazine and desmethyl-levomepromazine respectively (see text for further details)

Discussion

Drug levels in human brain

In man less than 1% of the oral dose of levomepromazine is excreted unchanged in the urine (Allgén et al., 1963). More than ten different metabolites of levomepromazine have been identified in urine from psychiatric patients receiving oral doses of the drug (Dahl and Garle, 1977; Johnsen and Dahl, 1982). However, even with highly sensitive and specific gas chromatographic-mass spectrometric methods, only five unconjugated levomepromazine metabolites could be detected in blood from psychiatric patients (Dahl and Garle, 1977; Dahl et al., 1982). Two of these, N-desmethyl-levomepromazine and levomepromazine sulfoxide reached higher steady state blood levels than unmetabolized levomepromazine in patients receiving oral doses of the drug (Dahl et al., 1982; Dahl, 1982). In contrast to levomepromazine sulfoxide, it is likely that mono-N-desmethyl-levomepromazine contributes to the antipsychotic as well as sedative effects of levomepromazine (Morel et al., 1987). Therefore, in the present study, levomepromazine and its desmethyl-metabolite have been measured in human brain tissue.

Plasma levels of levomepromazine under standard psychiatric therapy range between 15 and 156 ng/ml (Dahl et al., 1977; Tokunaga et al., 1997). With 50 mg twice daily plasma levels between 25 and 40 ng/ml ml were measured (Dahl, 1976). The patients in the present study received much lower doses of levomepromazine (range 6.25 to 37.5 mg/day). Although we were not able to measure peripheral drug concentrations they are expected to be below 25 ng/ml.

When comparing the brain concentrations measured here with plasma levomepromazine levels reported in the literature (Dahl, 1976; Dahl et al., 1977; Tokunaga et al., 1997),

the brain to blood concentration ratio derived is about 10 even after short-term treatment. These results are paralleled in animal experiments. Compared to blood levels, 17–33 fold higher concentrations of levomepromazine were found in rat brain tissue (Afifi and Way, 1968). Levomepromazine is a weak base and amphiphilic substance with a pKa-value of 9.2 (Martindale, 1993). Furthermore, levomepromazine is very lipophilic with a log P of more than 3 (El Ela et al., 2004). With these physicochemical characteristics, accumulation of levomepromazine in brain tissue is mainly due to solution in lipophilic structures and trapping in acidic intracellular compartments like lysosomes (Kornhuber et al., 1995; Daniel and Wójcikowski, 1997; Daniel et al., 2001; Daniel, 2003).

Accumulation of levomepromazine in lipophilic and acidic intracellular compartments might induce a wide range of changes in neuronal morphology and function. While such changes have not yet been investigated directly for levomepromazine, reports are available for other neuroleptic drugs, antidepressant drugs or opiates regarding subcellular structure (Bal and Smialowska, 1987; Bal-Klara and Bird, 1990; Sklair-Tavron et al., 1996), cell volume (Hoffmann and Simonsen, 1989; Hara et al., 1999) and neuronal function (Kornhuber et al., 1995).

Regional distribution

With this investigation for the first time, a region-specific distribution of a neuroleptic drug has been determined in the human brain. The main finding of the present investigation is an unequal distribution of levomepromazine in human brain tissue with high values in basal ganglia and the thalamus.

Since metabolic enzymes for xenobiotics have a region-specific distribution in the brain (Britto and Wedlund, 1992; Schilter and Omiecinski, 1993; Ravindranath et al., 1995; Norris et al., 1996) region-specific metabolization of levomepromazine (Hals and Dahl, 1994) may contribute to region-specific tissue uptake. Phenothiazines are hydroxylated by Cyp2D6 (Meyer et al., 1996). Compared to the neocortex, hippocampus und cerebellum, the Cyp2D6 activity is low in the basal ganglia of the human brain (Siegle et al., 2001). Another possible reason for the results presented here might be both a region-specific expression of P-glycoproteins and a region-specific carrier-mediated transport of drugs across the blood-brain barrier. However, levomepromazine shows only a weak binding to P-glycoprotein and was not identified as an P-glycoprotein substrate (El Ela et al., 2004).

It could be argued that the sequential cessation of cerebral blood flow during the agonal state might have secondarily produced the unequal regional distribution of levomepromazine and desmethyl-levomepromazine. Higher cerebral blood flow might induce a wash-out of the drug from brain tissue. But this is unlikely because the characteristic regional distribution was found in all patients investigated. Furthermore, cerebral blood flow should have ceased first in the basal ganglia and thalamus and then in cortical areas. During agonal status cerebral blood flow usually decreases in cortical areas. Finally, a preferential accumulation of neuroleptic drugs in basal ganglia has previously been found in experimental animals (Janssen et al., 1968; Laduron et al., 1978; Korpi et al., 1984).

Passive diffusion across concentration gradients is one main mechanism of *postmortem* drug redistribution (Hilberg et al., 1994). This mechanism should equalize region-specific differences with longer *postmortem* time. Thus, the region-specific differences of levomepromazine concentration found in this postmortem investigation might even be more pronounced *antemortem*.

The reasons for region-specific accumulation of levomepromazine in human brain tissue are not fully understood. Levomepromazine probably accumulates in neurons and not in astrocytes and white matter by binding to

phospholipids and by uptake to acidic compartments, mainly lysosomes. It has been shown that lysosomal trapping plays an important role in the neuronal uptake of thioridazine (similar pKa and log P values to that of levomepromazine), but is of marginal significance in astrocytes and white matter (Daniel et al., 2001). The phospholipid composition and density of lysosomes may vary in different brain regions (Sellinger and Hiatt, 1968; Daniel, 2003), which might explain the region-specific accumulation of levomepromazine.

Compared to uptake into the cell, binding of neuroleptic drugs to cell surface receptors probably does not largely contribute to the unequal distribution: the distribution of levomepromazine across brain areas does not follow the distribution of dopamine receptors or other binding sites. Furthermore, the number of cell surface receptors is small compared to the drug concentrations measured.

Considering the potential changes in neuronal structure and function described above, the region-specific accumulation of levomepromazine in human brain tissue might have parallels to several findings in neuroleptic treated patients, specifically basal ganglia enlargement and tardive dyskinesia.

Basal ganglia enlargements in schizophrenia have been repeatedly described both in *postmortem* brain (Heckers et al., 1991) and *in vivo* MRI (Chakos et al., 1995; Gur et al., 1998; Corson et al., 1999) studies. More recent evidence suggests that this enlargement is not related to the disease process itself but to neuroleptic drug treatment. This hypothesis is based on the results of sequential scanning studies in schizophrenic patients before and during neuroleptic drug treatment. This effect of neuroleptics on basal ganglia volumes is also found in patients with non-schizophrenic psychiatric illness (Doraiswamy et al., 1995) and in rat models (Chakos et al., 1998; Andersson et al., 2002). The reason for neuroleptic-induced volume increases is not yet understood; adaptive changes resulting from blockade of striatal dopamine receptors and changes in regional blood flow have been proposed (Miller et al., 1997a, b). The results presented here, i.e. preferential accumulation of a neuroleptic drug in basal ganglia, might help to understand this phenomenon.

The cause of tardive dyskinesia has been associated with neurotoxic properties of neuroleptic drugs. Basal ganglia appear to be particularly vulnerable to the neurotoxic action of neuroleptic drugs (Gunne et al., 1984). Higher concentrations of neuroleptic drugs in certain brain areas might lead to apoptosis or necrosis and might thus explain the regional differences in neuronal vulnerability, i.e. cell death due to prolonged administration of neuroleptic drugs in basal ganglia associated with tardive dyskinesia. The molecular mechanisms of neuroleptic-induced cell death might include oxidative stress, shifts in pH-balance and toxic effects of metabolites. Furthermore, it has been suggested that basal ganglia volume enlargement correlates with tardive dyskinesia (Chakos et al., 1998). The high concentrations and the long half-life of levomepromazine in human brain tissue found in the present study might thus give a further explanation for the neurotoxic effects of neuroleptic drugs.

Pharmacokinetic parameters

Due to the small number of patients investigated, it was only possible to roughly estimate the elimination half-life of levomepromazine and desmethyl-levomepromazine in human brain tissue. We found values of about one week and one month respectively. These values are considerably higher than values found in the periphery: the plasma elimination half-life of levomepromazine has been reported to range between 15 and 30 hrs (Dahl, 1976). Steady-state conditions are reached within 7 days of oral treatment. Levomepromazine concentrations have also been measured in the rat brain: after single

administration, levomepromazine levels in brain tissue were maximal at 1 hr and were still appreciable after 4 hrs (Afifi and Way, 1967). Over the 12-hour period investigated the half-life of disappearance of levomepromazine from brain tissue was slower than in blood (Afifi and Way, 1968). The results presented here, i.e. the long elimination half-life from brain tissue for levomepromazine and its desmethyl-metabolite, correspond to our previous investigation with haloperidol (Kornhuber et al., 1999).

One would expect that a drug with a long half-life of about one week will accumulate during several weeks. It is therefore unexpected that considerable levomepromazine concentrations in the human brain were found even after a single application of the drug. High levomepromazine brain to blood concentrations ratios have also been found in rats after a single dose of levomepromazine (Afifi and Way, 1968). A comparable rapid accumulation has been found with haloperidol both in human (Kornhuber et al., 1999) and rat brain (Sunderland and Cohen, 1987; Cohen et al., 1988). The acidotropism of weak bases like levomepromazine may contribute to these high blood to brain concentrations even after short-term treatment.

Conclusion

In conclusion, we directly measured concentrations of levomepromazine and desmethyl-levomepromazine under therapeutic conditions in postmortem human brain tissue. The drugs appear to accumulate in brain tissue relative to blood. There was a region-specific distribution of levomepromazine with high values in basal ganglia. If such a region-specific distribution holds true also for other neuroleptic drugs, it might increase our understanding of volume changes in basal ganglia with neuroleptic drugs and a preferential vulnerability e.g. observed in tardive dyskinesia.

The estimated elimination half-lifes in brain tissue are in the range of about one week and one month for levomepromazine and its metabolite, respectively. After two half-lives (about 2 weeks) there is still a considerable amount of levomepromazine in brain tissue. Patients exposed to levomepromazine cannot be considered free of residual effects of the drugs for a number of weeks, even after acute treatment and even when the drug concentration is below detection level in the blood.

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