and room temperatures. Propiverine (VEB Sächsisches Serumwerk, Dresden) was resolved with saline by 2 mg/ml, and injected i.v.

For cystometrography, 1.6 ml of saline was infused into the urinary bladder in 1 min. Immediately after starting infusion, vesical pressure began to rise, and reached a plateau in 15-30 sec. Subsequently, at least 1 sequence of rhythmical bladder constriction and urine excretion was observed. Vesical pressure decreased after infusion was stopped. As a parameter of this volume-pressure curve, P/V ratio was employed: P represents vesical pressure of the plateau; V represents the volume of saline infused until vesical pressure reached the plateau level. Figure 1 shows changes in P/V ratio by i.v. injection of 2 mg/kg propiverine. Volume-pressure curve was estimated every 10-20 min after propiverine injection. Mean and SE for 4 animals were demonstrated. Propiverine decreased the P/V ratio significantly at 10, 20 and 30 min after injection (Student's t-test, $p < 0.05$). The maximal decrease in P/V ratio was achieved 10 min after propiverine injection: P/V ratio decreased from 54.8 ± 6.1 to 29.5 ± 7.0. Actual P- and V-values were 38.4 ± 7.3 cmH_2O and 0.8 ± 0.2 ml in the control, and 30.0 ± 6.5 cmH_2O and 1.1 ± 0.1 ml at 10 min after drug application respectively.

In preliminary experiments, saline infusion was carried out at a rate of 0.3 ml/min until the 1st bladder constriction and urine excretion was observed. In the case of this slower infusion rate, infusion time was prolonged by approx. 1.7 times 15 min after propiverine injection, i.e. the saline volume necessary to cause excretion was increased by 1.7 times ($n = 2$).

The effect of propiverine on PNA during the excretory reflex was examined in 4 animals. In these experiments, the urinary bladder was continuously infused with saline by 0.6 ml/min. Vesical pressure above a certain level initiated burst of discharges in the efferent pelvic nerves, and vesical pressure and PNA proportionally increased and decreased during continuous infusion. As shown in figure 2, 2 mg/kg propiverine significantly decreased both vesical pressure and PNA (Student's t-test, $p < 0.05$). This shows that propiverine inhibited the excretory reflex of the urinary bladder.

In the present experiments, the following 2 results were obtained. 1. Propiverine decreased P/V ratio of volume-pressure curve of the rat urinary bladder. 2. Propiverine suppressed efferent nervous activity of the bladder branch of the pelvic nerve during vesical perfusion. As the P/V ratio is supposed to represent both mechanical and reflex properties of the bladder, a decrease in P/V ratio indicates a decrease in the contractile force of the bladder muscle and inhibition of neural components of the excretory reflex. Direct action of propiverine on bladder muscle has recently been proved in the isolated rabbit urinary bladder in vitro[4]. However, a possibility of central action of propiverine cannot yet be considered negligible, because of its inhibitory effects on nicotine-spasm and efferent pelvic nervous activity. Neurotropic action of propiverine will be further investigated. The present experiments showed that propiverine exhibits an inhibitory action on the urine expulsion of the rat, besides its spasmolytic and analgesic effects.

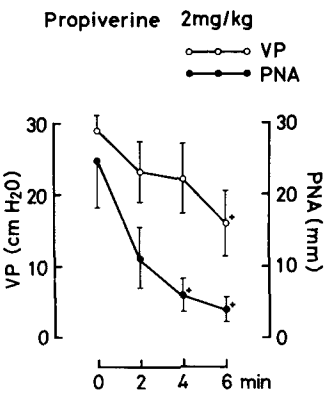

Figure 2. Effect of propiverine on vesical pressure (VP) and efferent pelvic nervous activity (PNA). Means and SE for 4 animals. PNA is shown as mm of recorder deflexion for integrated values. Propiverine, 2 mg/kg i.v.$^+$, data significantly different from those of control (Student's t-test, $p < 0.05$).

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Effects of macrolide antibiotics on barbiturate sleeping time in mice

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Summary. Triacetyloleandomycin and josamycin, when administered to inbred Balb/c mice orally twice daily at a dose of 12.5 or 25 mg per kg over 3 days, were found to increase barbiturate sleeping time significantly. In contrast, erythromycin ethylsuccinate, erythromycin propionate, midecamycin and spiramycin were devoid of any such activity under the same conditions.

The hazards of certain drug interactions with macrolide derivatives have been emphasized previously, particularly concerning ergotamine, the pill, carbamazepine and theophylline on the one hand, and triacetyloleandomycin on the other hand[1]. Available data suggest enzymatic inhibition as a likely mechanism[2]. The status of other macrolide antibiotics is poorly established in this context. In order to provide additional information, we undertook to study the influence of every macrolide marketed in France on barbiturate sleeping time, a good indicator of drug-metabolizing enzyme activities[3].

Methods. Inbred Balb/c mice weighing between 18 and 20 g were purchased from Iffa Credo (France) and randomly used throughout. Each experimental group consisted of 5 male and 5 female animals. Sleeping time was quantified by means of the righting reflex method[4]. In a first series of experiments, mice were given 12.5 or 25 mg/kg triacetyloleandomycin, erythromycin propionate, erythromycin

ethylsuccinate, josamycin, midecamycin, spiramycin or an equivalent amount of saline orally twice a day, over 3 days. 2 h after the last antibiotic administration, mice received an i.p. injection of pentobarbital (60 mg/kg). In a 2nd series, triacetyloleandomycin-and josamycin-treated mice were injected with sodium barbital (350 mg/kg, i.p.) and in a 3rd series, mice received 1 single oral dose of triacetyloleandomycin followed by i.p. pentobarbital after a varying time interval. Student's t-test was used for statistical analysis of results.

Results. Pentobarbital-induced sleeping time was found to be significantly increased after triacetyloleandomycin or josamycin pretreatment whatever the dose. Pretreatment with any of the other macrolide antibiotics proved ineffective. Barbital-induced sleeping time was not affected by either triacetyloleandomycin or josamycin. Finally, a single oral dose of 25 mg/kg triacetyloleandomycin 12 h before pentobarbital increased sleeping time significantly.

Effects of six macrolide antibiotics on barbiturate sleeping time

Tested drug	Oral dose	Sleeping time (mean ± SEM)
3 days pretreatment, last administration 2 h before pentobarbital		
Controls	–	122.0 ± 6.5
Erythromiycin ethylsuccinate	12.5 mg/kg	116.1 ± 4.9 (a)
	25 mg/kg	125.4 ± 4.9 (a)
Erythromycine propionate	12.5 mg/kg	120.8 ± 4.9 (a)
	25 mg/kg	126.6 ± 4.9 (a)
Josamycin	12.5 mg/kg	184.2 ± 9.2 (b)
	25 mg/kg	233.6 ± 6.1 (c)
Midecamycin	12.5 mg/kg	124.3 ± 4.5 (a)
	25 mg/kg	128.3 ± 3.2 (a)
Spiramycin	12.5 mg/kg	118.3 ± 4.0 (a)
	25 mg/kg	113.2 ± 4.2 (a)
Triacetyloleandomycin	12.5 mg/kg	188.0 ± 4.0 (b)
	25 mg/kg	188.9 ± 7.0 (c)
3 days pretreatment, last administration 2 h before barbital		
Controls	–	240.8 ± 10.4
Josamycin	12.5 mg/kg	225.4 ± 17.1 (a)
	25 mg/kg	217.7 ± 25.3 (a)
Triacetyloleandomycin	12.5 mg/kg	254.7 ± 18.2 (a)
	25 mg/kg	267.7 ± 23.4 (a)
1 single administration before pentobarbital		
Controls	–	122.0 ± 6.5
Triacetyloleandomycin		
2 h before pentobarbital	12.5 mg/kg	114.9 ± 6.0 (a)
	25 mg/kg	126.4 ± 5.0 (a)
12 h before pentobarbital	12.5 mg/kg	112.7 ± 5.2 (a)
	25 mg/kg	168.5 ± 6.1 (b)

Significance in comparison with control animals is expressed as (a) for $p > 0.05$, (b) for $p < 0.01$ and (c) for $p < 0.001$.

Discussion. Among the 6 macrolide derivatives studied, only triacetyloleandomycin and josamycin were found capable of increasing pentobarbital-induced sleeping time. That they did not influence barbital-induced sleeping time is in agreement with the proposed mechanism of an inhibition of drug metabolizing enzymes, as pentobarbital is transformed to an inactive metabolite while barbital is excreted mostly unchanged[3]. Our results are consistent with those of Lavarenne et al.[4] and Azria et al.[5] who did not find any pharmacokinetic interaction involving midecamycin and spiramycin respectively. Current data are more controversial with erythromycin derivatives[6,7] and josamycin[8,9]. It is apparent that triacetyloleandomycin-induced enzymatic inhibition develops very quickly, as previously suggested by clinical findings[1]; furthermore, the fact that triacetyloleandomycin given 2 h before pentobarbital does not influence sleeping time, although it increases it when given 12 h before, is in agreement with Pessayre et al.[2] who showed that triacetylolandomycin binds to cytochrome P 450, thus inactivating it. Finally, barbiturate sleeping time appears to be a valuable tool for predicting drug interactions mediated by liver enzymes, owing to the good correlation between our experimental findings and clinical data.

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On the complementarity of long repeated sequences in DNA to hnRNA[1]

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Summary. Long repeated sequences containing up to 18,000 base pairs were found in a human DNA fraction isolated with the nuclease S1-dioxane method. Hybridization studies showed that the long repeats contained a greater proportion of sequences complementary to hnRNA than short repeats. They also exhibited homology to the latter, as shown by cross-hybridization experiments.

In eukaryotic cells the lengths of the primary transcripts of DNA exceed those of mRNA by several fold, and deletion of intervening sequences appears to be necessary to the formation of many mRNAs[2,3]. Several studies have indicated the sequence heterogeneity of introns. Members of the *Alu* family and other short repeated sequences have been found in the regions flanking some genes[4]. Regions of the genome that do not contain repeated or foldback sequences have been identified in other introns[5]. These observations have not, however, accounted for the considerable length that must be possessed by some introns, if the size discrepancies between hnRNA and mRNA are to be explained.